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Trauma in Critically Ill Children: Transfusion and Osmotherapy Practices

par

Nadia ROUMELIOTIS

Programme de Sciences biomédicales

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This memoire entitled:

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Transfusion and Osmotherapy Practices

Presented by

Nadia ROUMELIOTIS

Was evaluated by a Jury composed of the following members:

Dr. Jocelyn Gravel
President Rapporteur

Dr. Guillaume Emeriaud
Supervisor

Dr. Jacques Lacroix
Co-supervisor

Dr. Yves Pastore
Member of the Jury

Summary (English)

Trauma is the leading cause of death of children, with the burden of mortality related both to traumatic brain injury and hemorrhagic shock. Despite the frequency of trauma in the pediatric population, the management of these patients is often based on adult literature due the sparse amount of literature in pediatric trauma. The studies presented below were intended to establish current practice, and prepare for future prospective studies in pediatric trauma.

The management of raised intracranial pressure (ICP) following traumatic brain injury (TBI) involves intracranial monitoring and the escalation of care to prevent secondary insults to the brain. Hyperosmolar therapy with mannitol (20%) and hypertonic saline (3%) are standard of care for the reduction of ICP, despite little evidence for their use. Our retrospective, single center study aimed to describe the clinical practice of hyperosmolar therapy in pediatric severe TBI, and its effect on ICP. We found that both mannitol and hypertonic saline are frequently used without a clear indication for one agent over another. There was insufficient power to confirm an effect on ICP, and multiple co-interventions given after boluses of hyperosmolar therapy may have contributed this lack of effect. In order to prospectively evaluate the effect of hyperosmolar therapy on ICP, a standardized approach to TBI care and hyperosmolar agents is necessary.

Red blood cell transfusion is a key component of the management of the unstable trauma patient. Literature now suggests that transfusion is associated with increased mortality, and practices have shifted toward restrictive transfusion strategies in many clinical populations. We sought to describe the transfusion practices in pediatric trauma patients based on a large previously conducted prospective study on blood loss in pediatric intensive care unit (PICU) patients. Compared to non-trauma patients, trauma patients were more likely to be transfused and transfused early in their course of stay. Younger age, higher PELOD and mechanical ventilation were associated with receiving a red blood cell transfusion in the PICU. Receiving a blood transfusion prior to PICU admission was most strongly associated with receiving a transfusion after PICU admission, suggesting ongoing bleeding in those transfused early.

Future prospective studies specifically designed for the above populations are necessary to improve medical practice, in order to improve the quality of the evidence based care provided to children.

Key words: Trauma, pediatrics, Traumatic Brain Injury, Hyperosmolar therapy, Mannitol, Hypertonic saline, Red blood cell transfusion, Anemia

Summary (French)

Les accidents sont la cause la plus fréquente de décès chez l'enfant. Les décès sont principalement dus aux traumatismes cranio-cérébraux (TCC) sévère et aux chocs hémorragiques. Malgré cela, la prise en charge de ces patients est souvent basée sur la littérature adulte.

Le mannitol et le salin hypertonique (3%) sont des traitements standards dans la gestion de l'hypertension intracrânienne, mais il existe très peu d'évidence sur leur utilité en pédiatrie. Nous avons entrepris une revue rétrospective des traumatismes crâniens sévères admis dans les sept dernières années, pour décrire l'utilisation de ces agents hyperosmolaires et leurs effets sur la pression intracrânienne. Nous avons établi que le salin hypertonique est plus fréquemment utilisé que le mannitol, qu'il ne semble pas y avoir de facteurs associés à l'utilisation de l'un ou l'autre, et que l'effet sur la pression intracrânienne est difficile à évaluer en raison de multiples co-interventions. Il faudrait mettre en place un protocole de gestion du patient avec TCC sévère avant d'entreprendre des études prospectives.

La transfusion sanguine est employée de façon courante dans la prise en charge du patient traumatisé. De nombreuses études soulignent les effets néfastes des transfusions sanguines suggérant des seuils transfusionnels plus restrictifs. Malgré cela, il n'y a pas de données sur les transfusions chez l'enfant atteint de traumatismes graves. Nous avons donc entrepris une analyse post-hoc d'une grosse étude prospective multicentrique sur les pratiques transfusionnelles des enfants traumatisés. Nous avons conclu que les enfants traumatisés sont transfusés de manière importante avant et après l'admission aux soins intensifs. Un jeune âge, un PELOD élevé et le recours à la ventilation mécanique sont des facteurs associés à recevoir une transfusion sanguine aux soins intensifs. Le facteur le plus prédicteur, demeure le fait de recevoir une transfusion avant l'admission aux soins, élément qui suggère probablement un saignement continu.

Il demeure qu'une étude prospective spécifique des patients traumatisés doit être effectuée pour évaluer si une prise en charge avec un seuil transfusionnel restrictif serait sécuritaire dans cette population.

Mots clés : Trauma, pédiatrie, traumatisme crânien, agents hyperosmolaire, mannitol, salin hypertonique, transfusion culot globulaire, anémie

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LIST OF ABBREVIATIONS

AABB	*American Association of Blood Bankers*
CaO2	Arterial Oxygen content
CHU	Centre Hospitalier Universitaire
CI	Confidence Interval
CO	Cardiac Output
CBF	Cerebral Blood Flow
CPP	Cerebral Perfusion Pressure
CT	Computed Tomography
DO2	Oxygen Delivery
ECMO	Extra-corporeal Membrane Oxygenation
GCS	Glasgow Coma Score
Hb	Hemoglobin
HR	Heart Rate
ICP	Intracranial Pressure
IQR	Interquartile Range
MAP	Mean Arterial Pressure
MODS	Multi Organ Dysfunction Syndrome
MOF	Multi Organ Failure
MSc	Master of Science
PALISI	Pediatric Acute Lung Injury and Sepsis Investigators
PaO2	Partial Pressure of Oxygen
PELOD score	Pediatric Logistic Organ Dysfunction
PICU	Pediatric Intensive Care Unit
PRISM score	Pediatric Risk of Mortality
RBC	Red Blood Cell
RCT	Randomized Control Trial
SaO2	Oxygen saturation

SCCM	*Society of Critical Care Medicine*
SD	Standard deviation
SV	Stroke Volume
TBI	Traumatic Brain Injury
TRALI	Transfusion Associated Lung Injury
TRIPICU	*Transfusion Requirements in Pediatric Critical Care Units*

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It takes a Village is an African proverb that leverages the belief that it takes an entire village to raise a child. So many people have supported me and been instrumental in my clinical and research career. These are few people from my village…

Dr. Jacques Lacroix first introduced me to clinical research. During a presentation to pediatric residents on the 'Programme Cliniciens Chercheurs' of which he is the program director, he suggested I complete a Masters during my clinical training in the pediatric intensive care unit. I thought the idea was quite crazy, but went home to reflect on it. Four years later, as I embark on pursuing Doctoral Studies in another university, I think it was the best advice he ever gave me. He is a model of scientific rigor, an expert scientist and methodologist, whose research has changed the practice of pediatric critical care. I consider myself very fortuitous to have Dr. Lacroix as a co-supervisor and mentor over the years, and he has no doubt contributed greatly the choice I have made to pursue research in my future career.

Dr. Renier, for taking a chance on me as a young student hoping to get into medical school, and giving me an opportunity by introducing me to laboratory research, thank you. No doubt my first publication in her laboratory opened multiple doors down the road. I am grateful.

And my supervisor, Dr. Guillaume Emeriaud. Few students are lucky enough to have a mentor as this one. An excellent scholar, physician, and researcher, he is in my opinion a model clinician-scientist. As a research supervisor, I thank him for his always open door, his constructive advice, his timely responses to all my inquiries and his perpetual smile. He is an exemplary scientist, who inspires patience, rigor and professionalism. I will look to him always for advice, in hopes to one-day work by his side.

I cannot thank my parents enough. My parents gave me everything. Most importantly, they gave me opportunities they never had. They have never stopped believing in me and never doubted me in the least. I am blessed to have inherited many of their tremendous qualities including my father's intelligence and my mother's perseverance. They have been the best role models a daughter could ask for. Thank you both.

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INTRODUCTION

Injury is the primary cause of morbidity and mortality in children. According to the National Vital Statistics of the Center for Disease Control, amongst all-cause mortality, 32% of children aged 1-9, and 39% of children over 10 years old, die of unintentional injury (1, 2). The burden of injury, weighted strongly by motor vehicle accidents, is primarily caused by traumatic brain injury (TBI) followed by hemorrhagic shock (3, 4). The treatment of these morbidities in trauma is the focus of this memoire.

Despite the enormous burden of trauma, little literature supporting evidence-based practice in pediatric trauma management exists. Children are underrepresented in clinical research, with practice management and guidelines that are often based on adult studies or expert opinion. In addition, adult studies frequently have much larger cohorts with consent much easier to obtain. Pediatric studies are often smaller, lengthier to conduct, and ethically more difficult to obtain consent for. In addition, the overall burden of disease is often perceived as lower in pediatrics. For the aforementioned reasons, research in pediatrics is often lacking and "children are not small adults".

Trauma also has multiple challenges with regards to research. Given the acute nature of trauma, studies involving trauma patients, and their management, frequently require deferred consent. It is often difficult to include patients in randomized controlled trials when clinical management is time dependent and critical. The ethical challenges surrounding consent in pediatric patients compound the difficulty of conducting prospective trials in trauma management.

Despite hurdles in research on evidence-based practice, the creation of clinical guidelines is widespread in medicine, in an attempt to standardize practice. Guidelines provide a common

framework for clinicians to adhere to similar practices, based often on the best available evidence or most expert opinion. Guidelines for the management of traumatic brain injury, and transfusion practices, are published based on varying degrees of evidence (5, 6). It has been demonstrated that adherence to these guidelines improves patient outcomes, and therefore their importance cannot be overstressed (7, 8). It is the strife for standardized practice based on good quality evidence that will truly begin to improve patient outcomes.

The focus of this memoire is improving the literature and knowledge of trauma care in the pediatric critical care population, with regards to the management of the largest burden of mortality; traumatic brain injury and hemorrhagic shock. The goal overall is to improve the quality of care we provide, and practice based on the best available evidence.

SECTION A. OSMOTHERAPY IN PEDIATRIC TRAUMATIC BRAIN INJURY

CHAPTER 1. INTRODUCTION TO TRAUMATIC BRAIN INJURY

1.1 TRAUMATIC BRAIN INJURY AND INTRACRANIAL HYPERTENSION

Traumatic brain injury (TBI) is the primary cause of mortality in children aged 6 month into adulthood (1). The severity of injury is classified according to the Glasgow Coma Scale (GCS), a clinical score on a scale of 3 to 15, designed to standardize the severity of neurological impact after trauma. It has been subsequently modified to accommodate the pediatric subpopulation (Figure 4). The GCS is inversely proportional to mortality (9). Mild TBI is defined as a score of >13, moderated TBI is a GCS of 8-13, and severe TBI is defined as a GCS < 8, with an associated mortality between 18-65% (10-13).

With regards to pathophysiology, an initial and definitive traumatic injury to the brain occurs during trauma, known as the primary hit. The goal of management of traumatic brain injury is to prevent any secondary injury to the brain from occurring, which worsen prognosis. The Monroe-Kellie hypothesis states that the cranium is incompressible, with a fixed volume, and therefore any increase in the volume of one compartment, decreases the volume of another compartment (Figure 5). In traumatic brain injury, inflammatory vasogenic and cytotoxic edema, as well as intracranial hematomas, result in raised intracranial pressure (ICP), defined as an ICP > 20mmHg. This intracranial pressure can therefore result in compression of brain tissue, shifting of brain structures, hydrocephalus, restrictive blood flow and/or possible cerebral herniation. Prolonged periods of intracranial hypertension have been associated with poor neurological outcome, and prompt management of high ICP is a cornerstone in the treatment of severe TBI.

The goal of TBI management is to avoid secondary injury to the brain, preventing any further cellular damage. This includes control of cerebral cellular metabolism, temperature control, glucose and electrolyte control, and adequate perfusion and oxygen delivery to tissues.

1.2 Intracranial Pressure (ICP) and Cerebral Perfusion Pressure (CPP) Monitoring

ICP monitoring involves the neurosurgical placement of an invasive catheter, in the ventricular or parenchymal portion of the cranium, to monitor the ICP (Figure 6). An intracranial pressure above 20mmHg is considered high in both adults and children.

The Cerebral Perfusion Pressure (CPP) is defined as the Mean Arterial Pressure (MAP) minus the Intracranial Pressure (ICP):

$$CPP = MAP - ICP$$

CPP therefore represents the net pressure gradient driving blood flow and oxygen delivery to brain tissue. Auto-regulation of cerebral blood vessels normally narrowly maintains cerebral blood flow (CBF), whereby hypertension causes cerebral vasoconstriction to avoid hyperemia, and hypotension causes cerebral vasodilation to avoid ischemia, in order to maintain constant blood flow to the brain within a set range of pressures. The minimal targeted CPP for adults is 50-70 mmHg, and minimum of 40 mmHg is accepted in small children (5, 14).

Guidelines for the management of severe TBI recommend sedation and monitoring of ICP for adults with persistent GCS ≤8 and abnormal head CT findings (14). In pediatrics, literature is poor and guidelines suggest that clinicians "may" monitor ICP for GCS ≤8, without mention of head imaging (5). Wide variability exists in the rate of ICP monitoring in pediatrics, ranging from 8% to 59%, with rates being significantly lower for infants (15-17). In preparation for the current study, we retrospectively reviewed reasons why ICP monitoring was not consistently undertaken in severe TBI at Sainte-Justine hospital. The overall proportion of ICP monitoring for

severe TBI was 39% from 2007 to 2014. Primary reasons for lack of monitoring were improving GCS (20%) and moribund status (20%), indicating that in most cases there was a justifiable reason for lack of monitoring as opposed to lack of adherence to guidelines [see Appendix 1](18). Nonetheless, monitoring of a persistently comatose salvageable child is widely considered standard practice (7, 8, 18).

1.3 Guidelines for the management of severe TBI – Hyperosmolar therapy

The primary goal in the management of severe TBI is to minimize any secondary impacts on the brain, known as second hits, to optimize the potential for recovery. After optimizing sedation, neuro-monitoring (for intracranial hypertension and seizures), temperature control, glucose and electrolyte control, hyperosmolar therapy is indicated for the treatment of persistently elevated ICP.

Hyperosmolar therapy (20 % mannitol or 3% hypertonic saline) is first tier therapy in intracranial hypertension management. The mechanisms of action of these agents are the reduction of blood viscosity and the reduction of cerebral intracellular fluid by oncotic movement of water into the intravascular compartment (19, 20). Further proposed theoretical mechanisms are increased cardiac output and volume expansion (21), stimulation of atrial natriuretic peptide (22), and restoration of normal cell volume and membrane potential for hypertonic saline (23). Hypertonic saline may have the added benefit of treating hyponatremia, which can be deleterious to the injured brain and can be associated with cellular swelling or cerebral salt wasting. Guidelines for the management of severe TBI in adults and children support invasive ICP monitoring and hyperosmolar therapy for raised ICP (5, 14). There is some adult literature suggesting that hypertonic saline is superior to mannitol for intracranial hypertension in TBI (24-28), however meta-analyses remain inconsistent (29, 30). Despite this ongoing debate, adult guidelines in 2007 from the Brain Trauma Foundation give a Level II

recommendation to mannitol, for the management of intracranial hypertension, as little literature was unavailable to support hypertonic saline use at the time (14).

In Pediatrics, the evidence for hyperosmolar therapy is very limited. Two small RCTs (n= 35 and n=18) of moderate quality demonstrated better control of ICP and less need for further interventions with hypertonic saline (3%) versus normal saline (31, 32). There are no prospective studies involving mannitol for ICP control in pediatric TBI, despite its widespread use in up to 50% of cases (15). Hypertonic saline therefore is a Level II recommendation for hyperosmolar therapy (doses 6.5ml/kg to 10 ml/kg) in pediatric TBI guidelines (5).

1.4 Statement of the problem

Despite its use for raised ICP since the early 20th century, the literature to support the use of hyperosmolar therapy in ICP reduction is virtually inexistent in children. There are no good quality studies demonstrating superiority of hypertonic saline versus mannitol in the reduction of ICP, or on clinical outcomes in pediatrics. Furthermore, the efficacy of both mannitol and hypertonic saline on reduction of ICP in children has not been clearly established. The current choice of agent for raised ICP in children is largely based on physician and center preference. As mentioned above, pediatric guidelines recommend hypertonic saline with Level II evidence based on little evidence, as no literature exists for mannitol (5).

1.5 Objective of Study and hypothesis

The objective of our study was to describe the use of hyperosmolar therapy in pediatric TBI, and evaluate the effects of 20% mannitol and hypertonic saline (3%) on Intracranial Pressure. We hypothesized that mannitol and hypertonic saline are used with equal frequency, and may reduce elevated ICP in the 2 hours post bolus, but suspect that isolating the specific effect of the hyperosmolar agent may be difficult.

CHAPTER 2. METHODS

2.1 STUDY DESIGN

We conducted a retrospective review of all severe traumatic brain injury patients admitted to the Centre Hospitalier Universitaire (CHU) Sainte-Justine in the last 7 years, in order to describe practice and use of hyperosmolar therapy in pediatric TBI. The study is an observational descriptive study with no intervention. Given the nature of the study design, patient consent was not necessary and the institutions' ethics review board approved the study.

2.2 SETTING

The CHU Sainte-Justine is a tertiary pediatric and maternal care center, and trauma center, located in Montreal, Quebec, Canada. The pediatric intensive care unit of Sainte-Justine admits approximately 1000 patients per year, and approximately 10 severe TBI patients. Given the geography of the province, trauma patients can be transported from as far as 7000 km away, requiring air transport and multiple stops at prior health care facilities. At the time of the study, there was no specific protocol for the management of severe TBI, and the treating medical team guided therapy.

2.3 POPULATION

All consecutive patients admitted between April 2007 and April 2014 to the pediatric intensive care unit (PICU) of CHU Sainte-Justine, were screened. Eligible patients were age 1 month to 18 years old, and had severe TBI as defined by GCS ≤ 8 on admission to the emergency department of Sainte-Justine. Specific inclusion criteria were invasive ICP monitoring, and administration of a hyperosmolar agent (20% mannitol or 3% hypertonic saline) thereafter, within 48 hours of PICU admission. There were no specific exclusion criteria.

2.4 INTERVENTION

In order to study the objective in this observational study, we evaluated boluses of osmotherapy as events. Each bolus of mannitol 20% or 3% hypertonic saline was recorded in the first 48 hours after PICU admission. Time of bolus, dose, volume and concentration were all recorded, to an arbitrary maximum of 10 boluses per patient. In addition to data on the bolus of osmotherapy, vital signs including heart rate, blood pressure (BP), Intracranial Pressure (ICP), and Cerebral Perfusion Pressure (CPP) were recorded at the time of the bolus and for the four hours following the bolus. ICP and CPP were recorded up to every 15 minutes when available. Temperature and diuresis were recorded every hour. All blood gases, serum sodium, osmolarity, and hemoglobin values were recorded for the 48 hours post admission. Infusions of sedation were recorded, along with changes in infusion rates.

2.4.1 Co-interventions

Co-interventions were defined as any therapy that could have an impact of the reduction of intracranial pressure in the 4 hours following a bolus of hyperosmolar therapy. For the purpose of this study, co-interventions included another hyperosmolar agent (mannitol 20% or 3% hypertonic saline), a bolus of sedation with a barbiturate or propofol, a hypertonic saline infusion, or a decompressive craniectomy. Intermittent boluses of fentanyl or morphine were not included in the co-interventions as they were too frequent in nature, and their effect would be temporally difficult to assess. Any repeat bolus of hyperosmolar therapy within 4 hours of the last bolus was recorded, along with its dose and concentration.

2.5 Outcome measures

2.5.1 Primary outcome

The primary outcome was the reduction in ICP, as measured by mean change in intracranial pressure after the hyperosmolar bolus. Pre-bolus ICP values were considered as time of bolus administration or within 15 minutes prior, and post bolus values were assessed on the hour, for the following 4 hours. When more frequent measures were present, hourly mean values were calculated.

2.5.2 Secondary outcome

Secondary outcomes measured included the effect of hyperosmolar therapy on mean arterial blood pressure (MAP), cerebral perfusion pressure (CPP), and serum sodium. In addition, the number of co-interventions post-bolus in each group was a secondary outcome, as a surrogate for therapy failure.

2.6 Sample size calculation

Sample size calculation for this retrospective review was performed using G-Power. We calculated the number of boluses of hyperosmolar therapy needed in each group (mannitol and hypertonic saline) in order to detect an intra-group mean change in ICP of 15% post bolus. In order to detect a mean difference of 15%, with a power of 80% and a bilateral alpha of 0.05, a sample size of 15 observations in each group was needed, with a calculated effect size of 1.06. The possible lack of independence of events was not taken into consideration for this study. Archive review indicated approximately 10-12 severe TBI admissions to the PICU annually. We elected to review the previous 5 years, considering most patients will have received both mannitol and hypertonic saline. Multiple patients not meeting inclusions, as well as many patients not receiving mannitol, led to the prolonging of an additional 2 years of review to gain in sample size and power. We therefore retrospectively reviewed the last 7 years of severe TBI admissions.

2.7 Data collection and analysis

Demographic data including time and mechanism of injury, head imaging, and referral from another center, were documented from charts. We described the use of hyperosmolar agents, 20% mannitol or 3% hypertonic saline bolus (or infusion), to a maximum of 10 boluses per patient in 48 hours. Several boluses were administered without elevated ICP, therefore to maximize potential for finding an effect, the impact on ICP and CPP was assessed following the first 2 boluses received only for an ICP > 20 mmHg. The measured change in ICP and CPP were recorded hourly for the 4 hours post bolus. Only the first two boluses were analyzed to minimize background noise and effect of co-interventions on ICP, which increased consistently over time in the PICU.

All data and vital signs were collected in paper charts until January 2013, and with electronic charting thereafter. Missing values at 4th hour (n=3 values) for ICP and CCP were treated by unit imputation. Co-interventions to control ICP (additional hyperosmolar agent, propofol, barbiturate bolus, decompressive craniectomy, and 3% hypertonic saline continuous infusion), and change in serum sodium were also documented. Pre-bolus sodium value was defined as the last value obtained within 6 hours prior to bolus, and post-bolus value was the first serum sodium between 1 and 6 h post-bolus.

2.8 Choice of Statistical methods

Descriptive data are reported in median (IQR = interquartile range), mean (± standard deviation), and n (%) where appropriate. Using SPSS, repeated measures ANOVA was used for analysis of trending continuous variables (i.e. mean ICP and CPP) with Bonferonni tests for comparison of means when significant. Non-parametric Mann Whitney test was used for comparison of baseline values. Paired t-test was used for comparison of pre- and post-quantitative values where *n* was sufficient. A p-value of 0.05 was used for statistical significance.

There was an insufficient sample size to compare the change in ICP between treatment groups (mannitol versus hypertonic saline), however this was not the objective of the study.

2.9 Author contributions

Nadia Roumeliotis performed all the data collection, aided in database design, contributed to statistical analysis, and drafted manuscript. Christian Dong performed data extraction, and aided with statistical analysis. Geraldine Pettersen and Louis Crevier contributed to study design, medical and surgical content, and correction of manuscript. Guillaume Emeriaud designed study, aided in database design, wrote initial protocol, oversaw statistical analysis, as well as corrections of final manuscript. All authors approved the final version of the article, and none have conflicts of interest.

CHAPTER 3. ARTICLE

The article below was submitted to the journal *Childs Nervous System* for peer review in April 2016.

Hyperosmolar Therapy in Pediatric Traumatic Brain Injury; a Retrospective Study

Nadia Roumeliotis[1], MD, Christian Dong[2] PhD, Géraldine Pettersen[1] MD MSc., Louis Crevier[3] MD. MSc., Guillaume Emeriaud[1] MD, PhD.

1. Department of Pediatrics, CHU Sainte-Justine 2. Research Center of CHU Sainte-Justine, 3. Department Neurosurgery, CHU Sainte-Justine, University de Montréal, Montréal, QC

Corresponding address:

Dr. Nadia Roumeliotis
Sainte-Justine Hospital, Rm 3444
3175 Cote Sainte-Catherine
Montreal, Québec
Canada H3T 1C5

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Keywords: Traumatic Brain Injury, Pediatric, Hyperosmolar Therapy, Mannitol, Hypertonic Saline, Intracranial Hypertension.

ABSTRACT

Objectives: To describe the use of hyperosmolar therapy in pediatric traumatic brain injury (TBI), and examine its effect on intracranial pressure (ICP) and cerebral perfusion pressure (CPP).

Design: A retrospective review of patients with severe TBI admitted to the pediatric intensive care unit (PICU) was conducted. Inclusion criteria were ICP monitoring and administration of a hyperosmolar agent (20% mannitol or 3% hypertonic saline) within 48h of PICU admission; for which dose and timing were recorded. For the first 2 boluses received for increased ICP (>20mmHg), the impact on ICP and CPP was assessed during the following 4 hours, using repeated measures ANOVA. Co-interventions to control ICP (additional hyperosmolar agent, propofol or barbiturate bolus), and serum sodium were also documented.

Setting: A tertiary care pediatric hospital center.

Patients: Children aged 1 month to 18 years, with severe traumatic brain injury (Glasgow Coma Score ≤ 8), and intracranial pressure (ICP) monitor.

Results: Sixty-four patients were eligible, of which 16 met inclusion criteria. The main reason for exclusion was lack of ICP monitor. Average age was 11 years (SD± 4) and median Glasgow Coma Score was 6 (range 4-7). One hundred and seven boluses were identified, and 70% percent [95% CI 64.0-74.3] of boluses were 3% hypertonic saline, with no identified baseline difference associated with this initial choice. Both mannitol and hypertonic saline were followed by a non-significant decrease in ICP (mannitol, p=0.055 and hypertonic saline, p=0.096). There was no significant change in CPP post bolus. A co-intervention occurred in 69% of patients within the 4h post hyperosmolar agent, and 8 patients received continuous 3% saline.

Conclusion: In pediatric TBI with intracranial hypertension, mannitol and 3% hypertonic saline are commonly used, but dose and therapeutic threshold for use vary without clear indications for

one versus another. Controlled trials are warranted, but several barriers were identified, including high exclusion rate, multiple co-interventions, and care variability.

Keywords : Traumatic Brain Injury, Pediatric, Hyperosmolar Therapy, Mannitol, 3% Hypertonic Saline, Intracranial Hypertension

INTRODUCTION

Traumatic brain injury (TBI) is the number one cause of death and morbidity amongst children aged 1 to 16 years (1). Severe TBI, defined as a Glasgow coma score (GCS) ≤ 8, typically requires aggressive management due to poor prognosis and high associated mortality. Intracranial hypertension is associated with poor outcome and increased mortality (2). Control of Intracranial Pressure (ICP) and maintenance of Cerebral Perfusion Pressure (CPP, defined as mean arterial pressure – ICP) are cornerstones in the management of severe TBI, with targets of <20mmHg and > 40mmHg (> 50 mmHg in older adolescents) respectively (3).

Hyperosmolar therapy (20 % mannitol or 3% hypertonic saline) is first tier therapy in intracranial hypertension management. The hypothesized mechanisms of action of these agents are the reduction of blood viscosity, and the reduction of cerebral intracellular fluid by oncotic movement of water into the intravascular compartment (4, 5). Guidelines for the management of severe TBI in adults and children (6), support invasive ICP monitoring and hyperosmolar therapy for raised ICP. Despite its use for raised ICP since the early 20th century, the literature to support hyperosmolar therapy in ICP reduction is virtually non-existent in children (3). There is some adult literature suggesting that hypertonic saline is superior to mannitol for intracranial hypertension in TBI, however meta-analyses remain inconsistent (7-13). Given this ongoing debate, adult guidelines do not suggest one agent over another (6). In pediatrics, there are no studies demonstrating superiority of hypertonic saline versus mannitol in the reduction of ICP, or on clinical outcomes. Furthermore, the efficacy of both mannitol and hypertonic saline on reduction of ICP in children has never been established. Hypertonic Saline (3%) has been shown to decrease co-interventions for ICP in 2 small randomized trials when compared to Ringer`s Lactate and normal saline (14, 15). The current choice of agent for raised ICP in children remains hypertonic saline according to guidelines (level II) as no article on the effect of mannitol met guideline inclusions (3). Use of hypertonic saline and mannitol remain to some extent, both

center and physician dependent. Indeed, studies have demonstrated a large variability in practice with regards to hyperosmolar therapy, dependent mostly on age and treating center (16, 17). Pediatric TBI guidelines have therefore stressed the need for further research on the efficacy of hyperosmolar therapy. The specific objective of our study was to describe the use of hyperosmolar therapy for severe TBI, and examine the effect of 20% mannitol and 3% hypertonic saline on ICP and CPP when administered for intracranial hypertension. The study is an essential first step to assess the feasibility, and prepare for a randomized controlled trial of hyperosmolar therapy for pediatric TBI.

MATERIALS AND METHODS

We conducted a retrospective review of all TBI patients admitted between April 2007 and April 2014 to the pediatric intensive care unit (PICU) of CHU Sainte-Justine, a pediatric and maternal tertiary care center, and a trauma center. The Institutional Review Board approved the chart review for this study. Eligible patients were age 1 month to 18 years old, had severe TBI as defined by GCS ≤ 8 on admission. Specific inclusion criteria were invasive ICP monitoring, and administration of a hyperosmolar agent thereafter, within 48h of PICU admission.

Demographic data, including time and mechanism of injury, imaging, and referral from another center were documented from charts. We described the use of hyperosmolar agents, 20% mannitol or 3% hypertonic saline bolus (or infusion), to an arbitrary maximum of 10 boluses per patient in 48 hours. The standard solution for hypertonic saline in our center is 3%. No standardized TBI protocol was in place for guidance of hyperosmolar therapy use. The impact on ICP and CPP was assessed for a 4 hour period following the first 2 boluses received for an ICP > 20 mmHg. Further boluses were not evaluated, given potential decreasing efficacy, unbalanced weighing of patients, multiple other co-interventions to control ICP, and overall background noise with concomitant therapy. All data and vital signs were collected in paper charts until

January 2013, and with electronic charting thereafter. Missing values at 4th hour (n=3) for ICP and CCP were treated by unit imputation, i.e. extrapolated from 3rd hour value. Co-interventions to control ICP (additional hyperosmolar agent, propofol, barbiturate bolus, decompressive craniotomy, and 3% hypertonic saline continuous infusion), and change in serum sodium were also documented. Pre-bolus sodium value was defined as the last value obtained within 6 hours prior to bolus, and post-bolus value was the first serum sodium between 1 and 6 h post-bolus.

Descriptive data are reported in median (IQR = interquartile range), mean (± standard deviation), and n (%) where appropriate. Using SPSS, repeated measures ANOVA was used for analysis of trending mean ICP and CPP, and post bolus, with Bonferonni tests for comparison of means when significant. Non-parametric Mann Whitney test was used for comparison of baseline values. Paired t-test was used for comparison of pre- post quantitative values where *n* was sufficient. A p-value of 0.05 was used for statistical significance.

RESULTS

Sixty-four patients were eligible, of which 16 met inclusion criteria and were included in the analysis (Figure 1). A high proportion of patients did not undergo ICP monitoring, either due to improving GCS or moribund status (18). Patient demographics and injury details are presented in Table 1. All ICP monitors were intra-parenchymal, except for two extra-ventricular drains used to evacuate cerebrospinal fluid.

Use of Hyperosmolar Agents

A total of 107 hyperosmolar boluses were recorded, with a median number of 6.5 boluses per patient (IQR 4.5-10, range 1-10). Seventy percent of boluses were 3% hypertonic saline and 30% were mannitol (Figure 2). All patients received 3% saline, while 3 never received mannitol. Given persistently high ICP, 3 patients had standing orders to alternate boluses of mannitol with 3% saline every 3 or 4 hours. No identified patient baseline characteristic was associated with

the initial choice of mannitol or 3% saline (Table 2), particularly with no statistical difference in age, GCS, Mean Arterial Pressure (MAP), or ICP. Pre-bolus serum sodium was also similar in patients who received 3% hypertonic saline as first bolus (141 mOsm/L ± 4) as compared to mannitol (139 mOsm/L ± 1).

Average doses of mannitol and 3% hypertonic saline given were 0.6 g/kg ± 0.2 and 1.8 ml/kg ± 0.7, respectively. Given the osmolarity of mannitol (1100 mOsm/L) and hypertonic saline (1027 mOsm/L), the average relative osmolar load for mannitol (3.5 Osm/kg ± 0.9) was therefore almost twice that of 3% saline (1.8 mOsm/kg ± 0.7). In addition to hyperosmolar boluses, 8 (50%) patients received a continuous infusion of hypertonic saline during the first 48h of admission. Initial 3% saline infusion rate was 0.5 ml/kg/h (IQR 0.5-0.7) initiated at a median of 10 hours (IQR 9-13) after admission.

Analysis of first two hyperosmolar boluses received

For the first two boluses of hyperosmolar therapy received for raised ICP (>20mmHg), both mannitol and hypertonic saline were followed by a decrease in ICP in the following 4-hour period, however this did not achieve statistical significance (mannitol n=8, p=0.055 and hypertonic saline n=14, p=0.096)(Figure 3a). There was no change in CPP post bolus (mannitol p=0.8 and hypertonic saline p=0.5) (Figure 3b). Serum sodium did not significantly change post mannitol or hypertonic saline (Sodium pre=140±2 vs. post=139±2 and pre=142±7 vs. post=142±6, p=0.94 and p= 1.0 respectively).

Co-interventions

Eleven patients (69%) received a co-intervention to decrease ICP within 4h post first hyperosmolar agent. Ten (62%) patients received another bolus of a hyperosmolar agent (mannitol or hypertonic saline) within a median time of 40 min (IQR 26-79), 2 patients received

a concomitant 3% saline infusion (after 140 min and 230 min), 2 patients received a propofol infusion (after 20min and 5 min) and 2 others received a thiopental infusion (after 1 min and 120 min).

DISCUSSION

This study describes the use and effect of hyperosmolar therapy, with mannitol and 3% saline, on ICP in pediatric TBI. Our findings illustrate the wide variability in practice and administration of these agents, and the trend toward a reduction in ICP associated with their administration, although this did not achieve statistical significance. The small sample size highlights the difficulty in conducting research on pediatric TBI patients. Severe TBI requiring ICP monitor and hyperosmolar therapy remains relatively uncommon, and multiple exclusions make large sample sizes lengthy to achieve. As previously published by our group, there are many patients who do not undergo ICP monitoring given extremely poor prognosis, or improving clinical neurological status (18). Nonetheless, this study provides new insights with regards to hyperosmolar therapy practices and the preparation for futures studies.

We found variability in the choice of hyperosmolar agent used, both initially and over the first 48h. In addition, both dosage and threshold ICP for use varied between treating physicians. Several patients received mannitol or 3% saline without having clearly elevated ICP (<20 mmHg), while others received agents in close succession for refractory intracranial hypertension. Bennett et al. have also reported wide variability in a retrospective database analysis of over 6000 pediatric TBI patients, with 33% of patients receiving hypertonic saline, 40% receiving mannitol and 28% receiving both (19). The use of hyperosmolar agents was associated with older age, more severe injury, intracranial hemorrhage and use of ICP monitor. They also noted a decrease in the use of mannitol after publication of the 2003 guidelines, and higher use of

hypertonic saline in cases of hyponatremia (20). A 2013 international survey of 34 centers revealed that despite similar ICP and CPP goals, medical management of raised ICP varies, and although 90% of centers use hyperosmolar therapy, concentrations of hypertonic saline range from 3% to 23% and certain centers never use either agent (18). In the present study, there did not appear to be a specific factor associated with the choice of mannitol or 3% saline for choice of agent, dose and osmolar load, threshold ICP, or use of continuous saline infusion. Contrary to our assumptions, initial serum sodium level did not seem to dictate the choice of first hyperosmolar agent; although hyponatremia, which may predispose to choosing 3% saline, was not observed in our series.

Both 3% hypertonic saline and mannitol were associated with decreases in ICP, although this did not achieve statistical significance. Importantly, causality is impossible to establish given the lack of a controlled environment and retrospective nature of the study. The observed trend could be the natural spontaneous evolution of the ICP, the effect of the hyperosmolar agents, or the consequence of multiple other factors. Several adult studies have evaluated hyperosmolar agents on ICP in TBI, but doses of both agents and results vary. Vialet et al. compared isovolumetric doses (2ml/kg) of 7.5 % saline and 20 % mannitol on ICP and found that hypertonic saline with higher osmolar load was more effective in controlling refractory ICP (9). Harutjunyan et al. found similar results in a randomized trial comparing 7,2% saline and 15% mannitol (8). When using equiosmolar dosing, Battison et al. (250 mOsm/dose mannitol and 7,5% saline) and Cottenceau et al. (20% mannitol at 4ml/kg, 15% saline at 2ml/kg) also concluded that hypertonic saline had a greater effect on ICP (12, 13). This difference was not reproduced however, by a randomized trial by Francony et al. and Sakelaridis et al. who found no difference between mannitol and hypertonic saline on ICP (10, 21). There are few studies on the effect of hypertonic saline or mannitol on ICP in pediatrics, and none has compared both agents.

A recent prospective study by Stein et al., and the only other study evaluating hyperosmolar therapy in pediatric TBI, demonstrated a decrease in ICP after hypertonic saline after correcting for cofactors. There was insufficient data to conclude on mannitol's effect on ICP (22). In our study, the effect of mannitol and hypertonic saline were not compared to one another, given the difference in osmotic load, small sample size and heterogeneity of both groups, which made them poorly comparable. The relatively higher osmolar load of mannitol compared to hypertonic saline in our study (3.5 versus 1.8mOsm/kg) may explain the lack of statistically significant decrease in ICP after both agents. Again, their effect on ICP has never been clearly demonstrated in pediatrics.

Serum sodium was surprisingly unchanged after hyperosmolar boluses. This is in contrast to the literature, which has consistently shown a significant increase in serum sodium after hypertonic saline (8, 9, 13, 23). It may be that the dose of hypertonic saline was generally quite low (average 1.8 ml/kg) and dose and concentration in the cited literature is often much higher (often 2ml/kg of 7.5 % saline or 5-10 ml/kg of 3% saline) (3).

There are other limitations to the study, especially given its retrospective nature. We were unable to control for hyperosmolar agents received prior to ICP monitor placement, in emergency department or operating room, and their effect on osmolarity, intravascular volume and viscosity, or ICP. Co-interventions contributing to the reduction in ICP were also difficult to account for, given multiple concomitant therapeutic interventions. All these variables could have diluted the expected effect of the agents. Although we examined the administration of additional hyperosmolar boluses, barbiturates, and propofol, we did not take into account small boluses of sedation (fentanyl, morphine, etc..), opioid and benzodiazepine sedative infusions and hyperventilation, as these were too frequent and/or transient in occurrence. All of the aforementioned agents however, potentially contribute to ICP reduction and therefore results

should be cautiously interpreted. In an attempt to limit the multiple co-interventions and confounders on ICP control, we only evaluated the first 2 boluses given for ICP > 20mmHg.

Future prospective controlled studies are necessary to establish the effectiveness of both mannitol and hypertonic saline in pediatric TBI. Prior to initiating prospective trials, issues regarding feasibility must be addressed. Multiple centers will be needed to gain enough power for accurate conclusion. Both inter- and intra-hospital variability in practice will require a standard protocol for ICP management. Specific criteria for invasive ICP monitoring are needed along with continuous electronic data collection, invasive arterial monitoring, temperature and position control, standardized ventilation, protocolized sedation, followed by an escalation with criteria for administration of a hyperosmolar agent. The hyperosmolar agents should be a standard dose per weight, and time of administration. Another difficulty in the feasibility of randomized controlled trials is rapid randomization and potential deferred consent needed, as agents are often rapidly administered after ICP monitoring.

CONCLUSION

The study is an important first step in the knowledge of hyperosmolar therapy for pediatric TBI. It is critical to understand our current practices, expected outcomes, and co-interventions, in order to prepare for future controlled studies. Several barriers were identified. In particular, we confirmed the difficulty in obtaining a large sample size due to the low incidence of severe TBI and the high rate of exclusion criteria. As seen in the other pediatric study (22), we observed a very high number of co-interventions to decrease ICP, which are potential confounding factors. Moreover, the practice variability was evident and should be addressed. In order to overcome those difficulties, a multi-center study would likely be required, with a step-wise standard sedation protocol for escalation in therapy, and defined criteria for administering

an additional hyperosmolar bolus. Providing equi-osmolar loads of both mannitol and 3% hypertonic saline would also be necessary to compare their effects on ICP reduction.

Despite widespread use of mannitol and 3% hypertonic saline for the management of raised ICP in TBI, there is no good evidence for their efficiency and indications in pediatrics. Good quality prospective data is crucially needed to support the recommendation of their use, and evidence based practice in neurocritical care in pediatric TBI.

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FIGURES

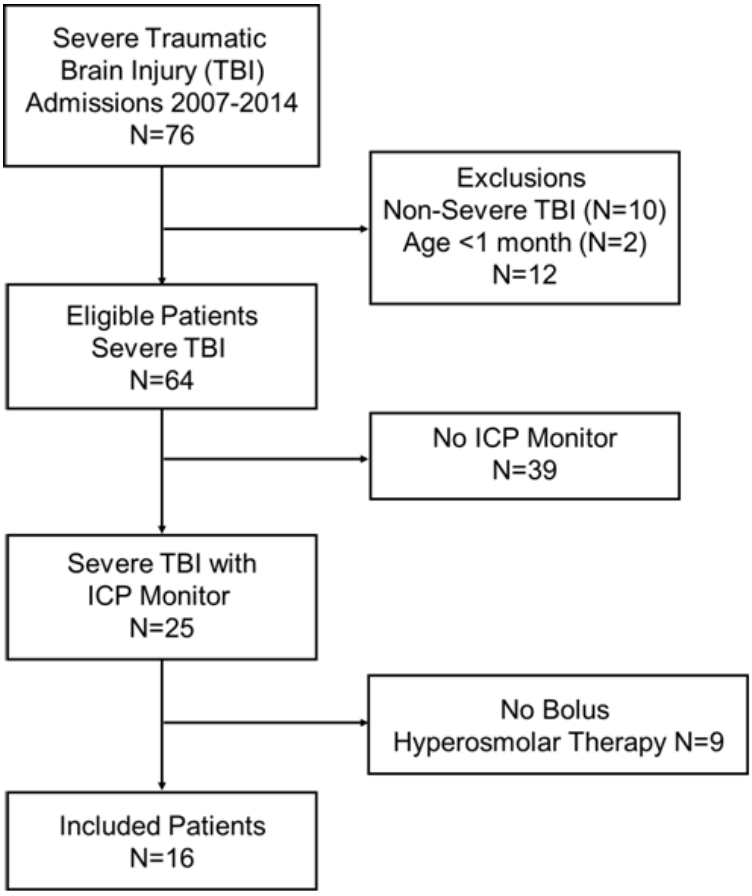

Figure 1. Flowchart of Patients included in Study.

TBI= Traumatic Brain Injury, ICP=Intracranial Pressure

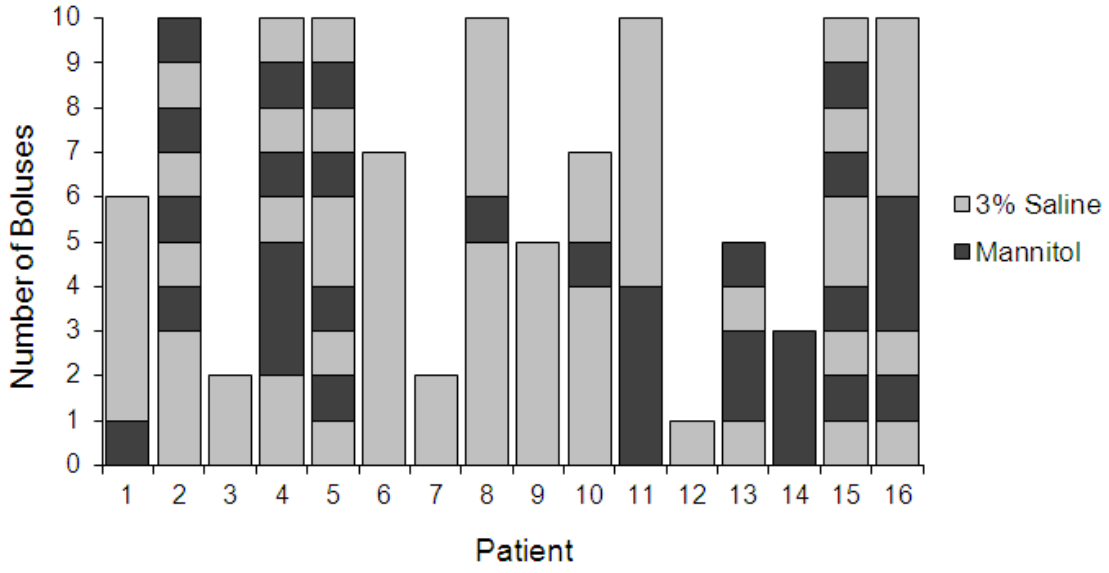

Figure 2. Number, type, and order of hyperosmolar agents given per patient in the first 48 hours (N=16). Data were censored after 10 boluses.

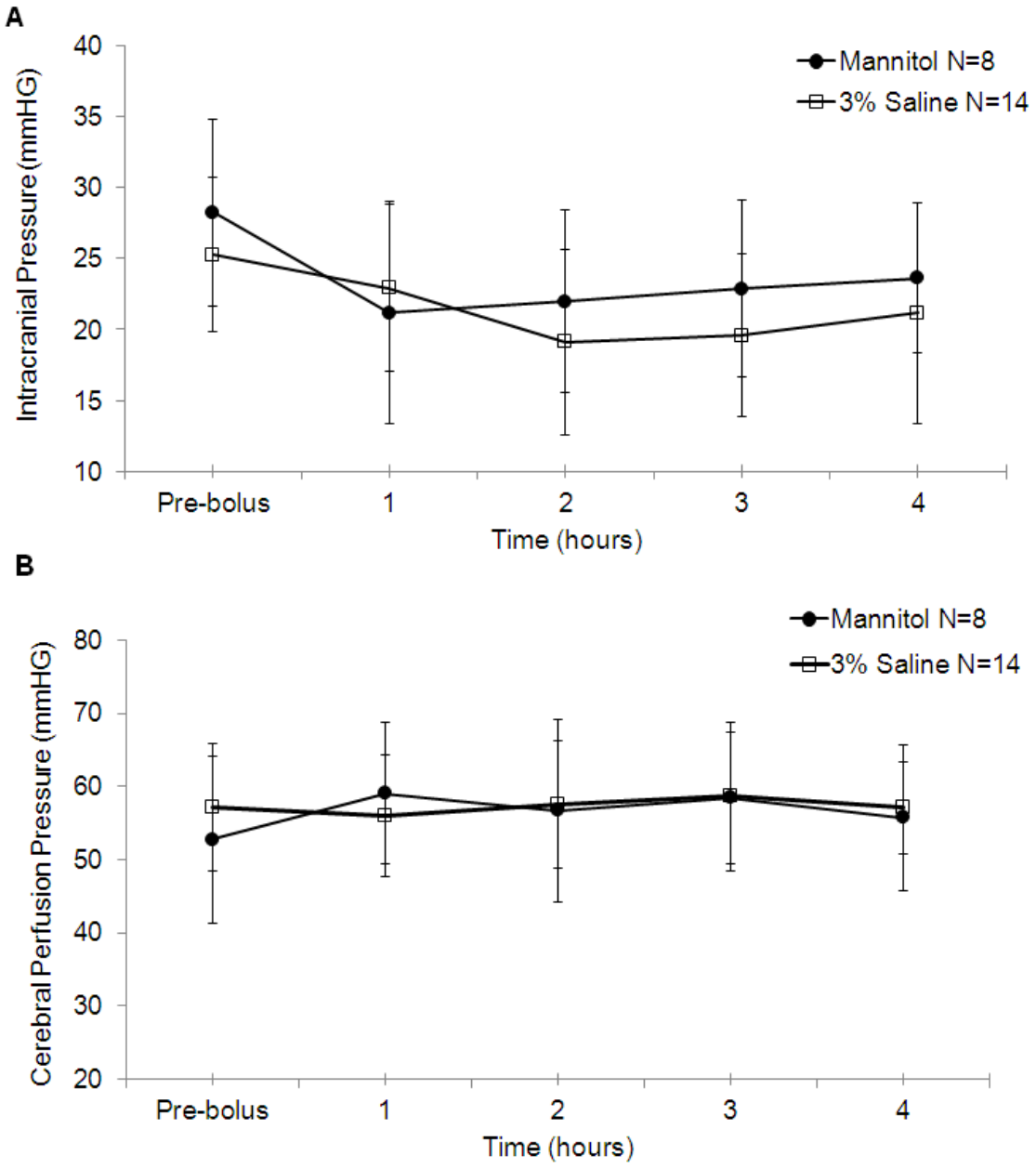

Figure 3. A. Change in intracranial pressure (ICP) and B. Change in cerebral perfusion pressure, after mannitol and 3% saline for intracranial hypertension (>20mmHg).

Table 1. Characteristics of patients.

Patient characteristic	**All patients (N=16)**
Age -years (median (IQR[a]))	13 (10-15)
Male sex (no. (%))	12 (75)
Weight- kg (median (IQR[a]))	48 (35-60)
Mechanism of injury (no. (%))	
Accident auto-pedestrian	1 (6)
Accident auto-bicycle	3 (19)
Accident auto-auto	5 (31)
Accident ATV[b]	2 (12)
Sport injury	1 (6)
Suspected abuse	1 (6)
Other	3 (19)
Glasgow Coma Score (median (IQR[a]))	6 (4-7)
Pediatric trauma score (median (IQR[a]))	4 (2-6)
Polytrauma (no. (%))	7 (44)
Time from injury to ER[c] min (median (IQR[a]))	196 (135-302)
Time from injury to ICP monitor min (median (IQR[a]))	435 (391-748)
Patients coming from another center (no. (%))	13 (81)
Head Imaging (no. (%))	
Epidural haematoma	2 (12)
Subdural haematoma	7 (44)
Intracerebral haematoma	5 (31)
Brain swelling	9 (56)
Basal cistern effacement	5 (31)
Deviation of median line	7 (44)
Decompressive craniectomy (no. (%))	3 (19)
External ventricular drains (no. (%))	2 (12)
Death (no. (%))	5 (31)

a : Interquartile range 25-75 percentile
b : All Terrain Vehicle
c : Emergency room at CHU Sainte-Justine

Table 2. Baseline characteristics of patients receiving mannitol or hypertonic saline as first 2 boluses

	Mannitol	**3% Saline**	**p value**
BOLUS 1	**N=3**	**N=13**	
Age (years)	11 (9-13)	13 (10-15)	0.7
Glasgow Coma Score	4 (4-4.5)	6 (6-7)	0.15
Intracranial Pressure (mmHG)	21 (17-25)	23 (19-28)	0.7
Mean Blood Pressure (mmHG)	76 (75-77)	84 (79-86)	0.2
BOLUS 1 & 2	**N=9**	**N=21**	
Intracranial Pressure (mmHG)	27 (22-32)	20 (19-26)	0.1
Mean Blood Pressure (mmHG)	78 (76-90)	82 (72-86)	0.8

Results presented in Median (IQR: Interquartile range 25-75 percentile)
Mann Whitney U Test used for independent means

SECTION B. TRANSFUSION PRACTICES IN PEDIATRIC TRAUMA

CHAPTER 4. INTRODUCTION

4.1 ANEMIA IN PEDIATRIC CRITICAL CARE

Anemia, defined as a reduced amount of red blood cells or hemoglobin (Hb) for age, is very common both in adult and pediatric critical care (33, 34). Reasons for this include disease state, bleeding, procedures, frequent blood sampling, inflammation, chronic illness and myelosuppression, amongst others. Red blood cells, and more specifically the hemoglobin within them, are critical for the transport of oxygen in blood to the tissues, and ensuring adequate oxygen content of blood (CaO2). Oxygen delivery (DO2) to tissues is dependent on arterial oxygen content (CaO2), a factor of hemoglobin and oxygen saturation (SaO2), and cardiac output (CO), a factor heart rate and ventricular stroke volume. The formula for delivery of oxygen is:

$$DO2 = CaO2 \times CO = [(SaO2 \times Hb \times 1.34) + 0.003 \times PaO2] \times [HR \times SV]$$

In normal physiological states, the delivery of oxygen to tissues is far superior to the demand. However in disease states, anemia, decreased oxygen saturation, reduced cardiac output and increased metabolic demand can all contribute to reduced oxygen delivery to tissues and cells. When the delivery of oxygen is insufficient to meet oxygen demand, tissue hypoxia results and cells move from aerobic metabolism to anaerobic metabolism.

There is no fixed threshold for transfusion of red blood cells in critical care. The AABB American Academy of Blood Bankers (AABB) and Society of Critical Care Medicine (SCCM) consensus recommends that transfusion must be given for a Hb < 5g/dL, and should be considered if the Hb is <7g/dL, but the level of evidence behind these recommendations is not optimal in trauma patients is li(6).

4.2 Harmful effects of Blood Transfusions

Over the past two decades the concept of « permissive anemia » has become standard practice, as the harmful effects of red blood cell transfusions have more clearly been demonstrated. Plasma rich blood products which include red blood cell transfusions contain inflammatory mediators including cytokines, complement activators, and oxygen free radicals that may initiate or enhance an inflammatory process. Complications of transfusions include febrile reactions, volume overload, transfusion associated lung injury (TRALI), allergic reactions, hemolysis, coagulopathy and multi-organ failure (MOF) (35, 36). In addition, the potential risk of infection transmitted through transfusion has been raised, although safety profiles of blood products have greatly increased and these infections are now virtually inexistent in developed countries. Complications related to blood storage also raise concern; including hyperkalemia, hemolysis, and hypocalcaemia from citrate toxicity.

In adult critical care, liberal transfusion strategy of red blood cells (<9 g/dL vs 7 g/dL) has been associated with an increased rate of cardiac events, pulmonary edema and myocardial infarction (37). In the PICU, patients having received red blood cell transfusion had associated longer days of invasive ventilation, increased mortality, and increased rate of nosocomial infections (34).

4.3 Transfusion Practices in Pediatric Critical Care

In pediatric critical care, Bateman et al. prospectively evaluated anemia and transfusion practices and found that 33% of children who stay at least two days in the PICU are anemic on admission to the PICU, and 41% develop anemia over the course of their stay, mostly due to frequent blood draws which average 5ml/day (34). In 2007, the TRIPICU study was published by Lacroix et al. demonstrating that a Hb of 7g/dL was non-inferior to 9.5 g/dL in critically ill

children that were stable (38). The publication changed pediatric transfusion practice, and transfusion thresholds decreased thereafter (39). Currently, guidelines support the recommendation that transfusion should be considered for patients with Hb between 5 and 7 g/dL, while most stable PICU patients with Hb >7 g/dL do not require a blood transfusion (6).

4.4 Transfusion in Trauma Patients

Hemorrhage is one of the leading causes of immediate death in the trauma patient, and the rapid recognition, and control, of bleeding is crucial to the management of these patients. Current guidelines by the American College of Surgeons, recommend rapid consideration of O negative (O-) blood transfusion in the unstable trauma patient after initial fluid bolus (3). Children, as opposed to adults, have a tremendous capacity to maintain blood pressure by raising their systemic vascular resistance, and therefore the recognition of critical hypovolemia and shock may be more difficult. Adult studies have demonstrated that trauma patients receiving blood transfusions have worse outcomes (40, 41). Restrictive transfusion strategies have never been applied to trauma patients as they are often considered unstable when needing a blood transfusion, and because clear determinants of blood transfusions in trauma have never been described.

4.5 Objective and Hypothesis

The objective of the study was to describe the red blood cell transfusion practices in pediatric trauma patients admitted to the critical care department. Our hypothesis was that trauma patients are transfused at a higher hemoglobin level, compared to other patients admitted to the PICU. Furthermore, it was expected that the study would provide a background for future studies and assess the feasibility of applying a restrictive transfusion strategy in this population.

CHAPTER 5. METHODS

5.1 COHORT STUDIES

Despite the fact that randomized controlled trials are the gold standard for testing certain hypotheses in medical research and to study the efficacy of therapeutic and preventative measures, they are impractical for a number of other research questions. When assessing the development of a disease or exposure, cohort studies are better suited for the comparisons of exposed and unexposed individuals. One cannot, for example, be randomized to anemia or to trauma.

A cohort study involves following a group of subjects though time, to assess the appearance of risk factors or risk markers and the development of certain outcomes, given a specific exposure. Analyses are then undertaken to assess if the exposure –the risk factor or the risk marker, is associated with the outcome by comparing exposed and un-exposed patients (42). For example, in a cohort of PICU patients the patients are all at risk of anemia (which can be an exposure) and subsequent transfusion (outcome). Furthermore, the transfusion can be assessed as an exposure, followed by the development of a complication (outcome). The features of the cohort studies allow one to make a temporal association between exposure and outcome, although causality may be impossible to establish.

5.2 THE BATEMAN STUDY METHODOLOGY

The database used for the current study, which was funded by Johnson & Johnson and monitored by the Food and Drug Administration, was developed to conduct the largest prospective, multicenter, observational cohort study on anemia in critically ill children in the United States and Canada. The quality of the subgroup analysis therefore depends on quality of

the original methods. The methods of the original study by Bateman et al. entitled *Anemia, Blood Loss, and Blood Transfusions in North American Children in the Intensive Care Unit* will be outlined below, and the original paper is indexed in Appendix 2.

5.2.1 Objective of the Study

The objective of the Bateman study was to evaluate the epidemiology of anemia and blood transfusions in critically ill children in North American, as well as determine the causes of ongoing blood loss in the PICU.

5.2.2 Study design

A large international multicenter observational study was undertaken in 30 PICUs across North American that were members of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) network in 2004-2005. The study design was a prospective cohort of all consecutive patients admitted to the PICU for over 48 hours, in order to describe the development of anemia and the transfusion practices amongst them. There was no specific intervention given the study design, and participation did not require any change in routine medical practice. A predefined sample size of 1000 patients was targeted for inclusion, after which point enrolment ended.

5.2.3 Study Population

All consecutive children admitted to the PICU, below 18 years of age were eligible for enrolment once admitted for over 48 hours. Patients were included if they had been admitted to the PICU over 48 hours and had no exclusions. Exclusions from the study were premature neonates, previous participation in the study, family history of refusing blood transfusion, pregnancy, involvement in other transfusion related studies, impending brain death and recent admission (within 7 days) to the PICU for more than 72 hours.

5.2.4 Data collection

All information after the first 48 hours was prospectively collected whereas the information on the first 48 hours of admission (day 1 and day 2) was collected retrospectively. Demographic data, admission diagnosis, comorbidities, and severity scores (PRISM III, PELOD) were recorded on admission (see Appendix 3 for specifications). All laboratory values pertaining to transfusion (hemoglobin, hematocrit) were included. Information on number and volume of blood draws were included daily. All complications and changes in patient status were recorded daily including mechanical ventilation, inotropic support, specific technologies (ECMO, renal replacement therapy) and surgery. For every transfusion given, pre-transfusion hemoglobin and physician reasons for transfusion were recorded, along with volume, storage time and type of transfusion.

5.3 Methodology for Subgroup analysis

Subgroup analysis involves evaluating a smaller group of individuals from the original cohort study and comparing them to the group based on exposure status (42). In the Bateman study, a subgroup of 99 trauma patients was included in the cohort, as defined by their diagnosis on admission. The trauma subgroup was then compared to the rest of the PICU cohort. Because the subgroup analysis was not considered *a priori*, trauma mechanism, location of injury, and solid organ damage were not recorded in the original study, and this information was not available.

5.3.1 Patient Population

The subset of patients included in the original Bateman study with diagnosis of trauma on admission constituted the trauma group in our analysis. The trauma subgroup was compared to the rest of the original cohort of PICU admissions. Transfusion thresholds for cardiac surgery

patients (43) and patients with cyanotic heart disease are known to be high (44). In order not to bias the comparison group toward a higher transfusion threshold, these patients were excluded. Therefore, all patients admitted with elective cardiac surgery, and all patients with known cyanotic heart disease were excluded in our analysis.

5.3.2. Outcomes

The main outcome variables assessed were transfusion variables, in order to evaluate the determinants of receiving a red blood cell transfusion in the PICU. We assessed pre-transfusion hemoglobin levels, number of transfusions, dates of transfusion in both trauma and non-trauma patients, along with demographics for trauma patients and factors that may be associated with a blood transfusion. Complications were recorded along with the time relevant to receiving a transfusion.

5.3.3 Data collection

Dr. Lacroix, as a co-author of the original Bateman study, provided access to the original database. Statistician T. Ducruet extracted desired data from the database, and oversaw the statistical analyses. No additional data was required or requested.

5.3.4 Statistical Analysis

The study is a prospective cohort and is descriptive in nature. Results are expressed in descriptive terms; mean (SD), median (IQR), number of patients (%) where appropriate. Comparison of means was performed with chi-squared test for outcomes with categorical values, and Student *t* test was used for continuous predictors. The proportion of transfused patients was plotted against pre-transfusion hemoglobin level to compare pre-transfusion thresholds between trauma and non-trauma patients. Multivariate logistic regression was used to predict

determinants of transfusion in trauma patients. The outcome (transfusion) was found in 56 patients; therefore we limited the number of variables to 5-6 variables included in the multivariate regression. This was in order to respect the rule of thumb that analysis should not include more than one possible risk factor per 10 events. The factors that were included in the multivariate analysis model include age, pre-transfusion hemoglobin, and factors found to be significant on univariate analysis; including transfusion prior to admission, PELOD score, and presence of active bleeding.

5.4. AUTHOR CONTRIBUTIONS

Nadia Roumeliotis wrote study protocol, obtained ethics approval, contributed to study design and drafted manuscript. Thierry Ducruet performed data extraction from the original database, and most statistical analyses. Scot Bateman and Adrienne Randolph provided access to database, oversaw article content and corrections. Jacques Lacroix and Guillaume Emeriaud provided access to the database, contributed to study design, oversaw and corrected manuscript.

CHAPTER 6. ARTICLE

This article was submitted to *Transfusion* in May 2016, and response is currently pending.

Determinants of Red Blood Cell Transfusion in Pediatric Trauma Patients admitted to the Intensive Care Unit

Nadia Roumeliotis[1], MD, Thierry Ducruet[2], MSc, Scot T. Bateman[3], MD, Adrienne G. Randolph[4], MD, Jacques Lacroix[1], MD, FRCPC, FAAP, Guillaume Emeriaud[1], MD, PhD, and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network.

1. Division of Pediatric Critical Care Medicine 2. Research Center of Centre Hospitalier Universitaire Sainte-Justine, Université de Montréal, and QC, Canada 3. University of Massachusetts Medical School, Worcester, MA 4. Division of Critical Care Medicine, Department of Anaesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Boston, MA, USA.

Corresponding Author:

Dr. Nadia Roumeliotis

Sainte-Justine Hospital, Rm 3444

3175 Cote Sainte-Catherine

Montréal, Québec

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ABSTRACT

Objective: Describe red blood cell (RBC) transfusion practices in pediatric trauma patients admitted to a pediatric intensive care unit (PICU).

Design: Post-hoc analysis of a prospective, 6-month observational study in 30 PICUs.

Population: Patients <18 years of age admitted to the PICU > 48 h were included. Cardiac surgery and cyanotic heart disease were excluded.

Results: Five hundred and eighty patients were enrolled in the study, of which 95 were trauma patients. Trauma patients were more frequently transfused prior to PICU admission ($p<0.001$), were older ($p<0.0001$) and more frequently mechanically ventilated ($p=0.05$). In the PICU, trauma patients were also more likely to receive a transfusion (55% vs. 37%, $p<0.001$) despite admission hemoglobin being similar in both groups ($p=0.86$). The mean pre-transfusion hemoglobin in the PICU was 9.0 g/L (SD 2.4) for trauma patients compared with 8.3 g/L (SD 2.4) for non-trauma patients ($p=0.09$). Amongst trauma patients, transfusion was associated with younger age, higher PELOD, mechanical ventilation, bleeding and transfusion prior to PICU. Multivariate regression analysis demonstrated that receiving an RBC transfusion prior to admission was strongly associated with receiving a blood transfusion in the PICU ($p=0.008$).

Conclusion: Trauma patients are at high risk for receiving a RBC transfusion both prior and during their PICU stay, despite a similar transfusion threshold compared to non-trauma patients. Transfusion prior to PICU admission is a strong determinant, suggesting ongoing bleeding requiring re-transfusion. Further studies designed for trauma patients are needed to evaluate the specific determinants of transfusion, in order to safely consider restrictive transfusion strategies in this group.

Keywords: Trauma, Pediatrics, Transfusion, Erythrocyte, Red blood cell, Critical care, Risk factor

INTRODUCTION

Injury is the leading cause of mortality in children over 1 year of age, with traumatic brain injury and hemorrhagic shock being the primary causes of death amongst them (1-3). Red blood cell (RBC) transfusion is an important component in the acute management of the unstable or bleeding trauma patient. Furthermore, anemia is very common in pediatric intensive care unit (PICU) patients (4). Despite the risks associated with severe anemia, increasing data suggest that significant risks are associated with transfusion (5, 6). Both adult and pediatric critical care practices have shifted to restrictive transfusion strategies given the potential adverse outcomes associated with transfusions (5, 6).

Transfusion guidelines for adult trauma cases recommend RBC transfusion for hemorrhagic shock, or hemodynamic instability with acute hemorrhage, otherwise suggest transfusion for Hb <7 g/dL in resuscitated trauma cases (7). Given the risks associated with on-going hemorrhage, trauma patients may not be subject to a restrictive transfusion strategy. Adult literature has shown that blood transfusion in trauma patients is common (10-23%), and an independent predictor of mortality and prolonged ICU length of stay (8, 9). A survey on the stated clinical practice and determinants of RBC transfusions amongst pediatric critical care practitioners revealed that high PRISM score, active bleeding and surgery, were statistically significant predictors of receiving a blood transfusion while in PICU (10), and a more recent survey reported mean (SD) transfusion threshold hemoglobin of 8.1 ± 1.2 g/dL for trauma cases (11). Literature however, on the observed transfusion practice in severe pediatric trauma is lacking.

The objective of the current study is to describe the RBC transfusion practices in pediatric trauma patients admitted to the PICU, and to characterize the determinants of RBC transfusion in this population. We hypothesize that trauma patients are transfused at a higher hemoglobin than non-trauma patients.

METHODS

This study is a post-hoc analysis from the dataset of a previous large multicenter prospective cohort (4).

Study population and Sites

The original cohort study was prospectively conducted in 30 American and Canadian PICUs that are members of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, for 6 months from September 2004 to March 2005. All consecutive patients younger than 18 years of age, admitted to the PICU for over 48 hours, were eligible. Exclusions from the original study included premature neonates, prior involvement in the study, family history of refusing blood transfusions, involvement in another transfusion study, pregnancy, impending brain death, and admission to the PICU for more than 72 hours in the last 7 days. Further exclusions for the purpose of the present study included all patients admitted for cardiac surgery, and patients with cyanotic heart disease, as both groups of patients are known to be associated with higher transfusions thresholds (12, 13). The institutional ethics committee approved the current study (#3997) with a waiver of consent as no new information was collected from patients.

Data collection and management

Given that patient inclusion occurred 48 hours after PICU admission, all data in the first 48 hours of admission were collected retrospectively (except blood loss data which was captured prospectively from admission in all patients). Trauma patients were identified from database based on the reason for PICU admission. Data collected on admission included: demographics, severity of illness as estimated by Pediatric Risk of Mortality (PRISM) III score, severity of organ dysfunction as estimated by Pediatric Logistic Organ Dysfunction (PELOD) score, transfusions prior to admission and baseline hemoglobin (Hb). All data after the first 48 hours of admission,

including blood loss information, blood transfusion information, clinical parameters, reasons for transfusion, laboratory values (hemoglobin) and complications were collected prospectively. Only events that happened after the first RBC transfusion in PICU were considered as possible transfusion-related complications in order to prevent any protopathic bias.

Statistical Analysis

Results of descriptive statistics were expressed as a fraction of the total population, mean ± standard deviation (SD), or median with interquartile range (IQR) where appropriate. Categorical variables were analyzed using Chi-square statistics. Continuous variables were compared using analysis of variance (ANOVA) test for normally distributed variables, and Wilcoxon test for discrete variables not normally distributed. P-value of 0.05 was chosen as statistically significant. Multivariate analysis was performed on factors found to be significant ($p<0.05$) in univariate analysis, with no interaction and that were not redundant, up to a maximum of 5 variables. Results are reported as odds ratio (OR) and confidence intervals (CI). All statistical analyses were done by a biostatistician (TD), using SAS statistical software.

RESULTS

Of the 977 patients included in the original study, 580 patients had no exclusion criteria and were included in the analysis, of which 95 were trauma patients and 485 were non-trauma patients (Figure 1A).

Trauma vs. non-trauma patients

Demographics for trauma and non-trauma patients are described in Table 1A. Compared with non-trauma patients, trauma patients were statistically more likely to be older ($p<0.001$) and mechanically ventilated ($p=0.05$). Baseline PELOD and PRISM scores were similar in both groups, as well as need for inotropic support. Trauma patients were more likely than non-trauma patients to have hemorrhagic shock ($p<0.001$), and they received more blood transfusions prior

to PICU admission (57% trauma group vs. 38% non-trauma group, p<0.0001). In addition, trauma patients were more likely to receive a transfusion during PICU course (55% vs. 38%, p=0.002), despite similar baseline admission hemoglobin levels in each group (11.3 g/dL vs. 11.1 g/dL, p=0.86) (Table 1). Mean pre-transfusion hemoglobin in the PICU was 9.0 g/L (±2.4) in the trauma group and 8.3 g/L (± 2.4) in the non-trauma group (p= 0.09), with a proportionally similar distribution of pre-transfusion hemoglobin (Figure 2A).

Transfusion practices in trauma cases

Amongst the 95 trauma cases, transfused patients were more likely to be young (p=0.02), with higher PELOD score (p=0.03), mechanically ventilated (p=0.04), and have active bleeding (p=0.053) on admission (Table 2). Transfused patients were also more likely to have received a transfusion prior to admission to PICU (p<0.0001). In the PICU, mean pre-transfusion hemoglobin was 9.0 g/L (SD 2.4) in the transfused trauma group, as compared to nadir hemoglobin of 9.8 g/L (SD 2.2) in the non-transfused trauma patients (p=0.053) (Table 2A). There were 8 cases of shock, 7 of which were hemorrhagic, and all were transfused. Head injury was not associated with receiving a blood transfusion in trauma patients. Multivariate logistic regression analysis revealed that being transfused prior to PICU was strongly associated with an increased likelihood for receiving a transfusion in the PICU (odds ratio: 17.7; CI 2.1 to 147.4, p=0.008) (Table 3A).

The majority of transfused trauma patients (n=30, 58%) received their first transfusion in the first 24 hours after PICU admission (Table 4A). The median number of units transfused was 1, but 8 patients (15%) required more than 5 RBC transfusions. The incidence rate of transfusion events was 1.5 per trauma case. Median length of storage of transfused RBCs was 14 days (IQR 9-21). Stated reasons for transfusion are presented in Table 5A. The primary reason for transfusion in trauma patients was low hemoglobin (44%), emergency surgery (9%) and acute blood loss (6%). In non-trauma patients, the primary reason for transfusion was also low

hemoglobin (39%), followed by a large variety of other reasons, including extracorporeal membrane oxygenation (ECMO) and aiming to increase oxygen delivery.

Outcomes and Complications

Table 6A reports adverse events observed during the entire PICU stay in transfused and non-transfused trauma patients. P-values are not presented as values are descriptive, and the two groups are poorly comparable. There were no deaths amongst all 95 trauma patients included in the study.

DISCUSSION

In our study, trauma patients were more likely to be older and mechanically ventilated compared to non-trauma patients, but with similar severity scores and inotropic support. Furthermore, trauma patients admitted to the PICU had a higher likelihood of receiving a RBC transfusion prior to PICU admission, despite similar baseline hemoglobin levels compared to non-trauma patients. Following PICU admission, trauma PICU patients are more likely than non-trauma patients to receive a blood transfusion (55% vs 37% respectively, $p<0.001$) even though their hemoglobin level was similar at PICU entry ($p=0.86$) and pre-transfusion in PICU ($p=0.09$). Amongst trauma patients, transfusion was associated with younger age, higher PELOD, mechanical ventilation, active bleeding and transfusion prior to PICU. These findings suggest that trauma patients may already be subject to a restrictive transfusion strategy, or more likely that they bleed rapidly, requiring subsequent transfusion prior to and on arrival to PICU.

Amongst pediatric trauma patients admitted to the PICU, the likelihood of RBC transfusion increases as the severity of injury increases (12, 14), with the incidence rate of transfusion in pediatric trauma patients ranging from 5% to 30% (15-17). We observed an incidence rate of 54.7%. This higher incidence of transfusion may be due to data collected prior

to the TRIPICU study of restrictive transfusion practices in critically ill children (6), or overall sicker patients given inclusion only of patients admitted > 48h in PICU.

Predictors of transfusions in adult trauma patients include low hematocrit, indices of shock (lactate and base deficit), low Glasgow Coma Score, and penetrating trauma (9, 18, 19). A retrospective study in all pediatric trauma patients by Allen et al. reported that hematocrit, glascow coma score (GCS), base deficit and Injury Severity Score (ISS) were associated with receiving a blood transfusion, with hematocrit remaining an independent predictor on multivariate analysis (16). Our predictors of RBC transfusion, in severe trauma patients admitted to the PICU, include young age, severity of illness measured by PELOD score, and transfusion prior to admission, with the latter being strongly associated in multivariate analysis. This suggests that in severe trauma patients, transfusion before likely means transfusion after PICU admission. Bleeding therefore, whether visible or occult, must be suspected and managed rapidly as suggested by Advanced Trauma Life Support management (20).

Despite the above predictors, both the surgical and resuscitative management of trauma patients is moving toward more conservative management, with increasing evidence for harmful effects of interventions in trauma. In terms of surgical care, current standard of care in stable patients with solid organ injury is non-operative management, a practice initiated by the pediatric population (21-25). A randomized controlled trial evaluating liberal vs. restrictive fluid strategies in trauma suggested that initial liberal fluid management might be harmful (26). The harmful effects of blood transfusion have also been established in adult trauma patients (8, 27, 28), and more recently in pediatrics (17). Hasan et al. previously reported an increased risk of adverse events, including mechanical ventilation and mortality, in pediatric trauma patients having received a blood transfusion (17). Nosanov et al. demonstrated that in a group of

massively transfused pediatric trauma patients, mortality was related to neurologic injury and coagulopathy (15). Multiple adult studies have also suggested harmful effects of transfusion in traumatic brain injury (TBI) patients, despite the evidence suggesting that anemia is detrimental in TBI (29,30). It is unclear however, that transfusion practices have changed significantly in pediatrics, in trauma and in the intensive care unit. A recent study by Klaus et al. concluded that pediatric transfusion triggers remain above 7 g/dL, and vary widely (> 2.5 g/dL) within and between pediatric subspecialties (31). No literature currently exists specifically for transfusion in trauma patients, let alone changes in transfusion practice. This study should therefore serve as a baseline for transfusion practice in pediatric trauma.

In terms of adverse events, we described that re-intubation, fluid overload, cardiac dysfunction and non-hemolytic fever, are relatively frequent after patients received blood transfusions in the PICU. Despite wide distribution, length of stay was longer in transfused group. These results must be interpreted with caution because our sample size is small, and unadjusted for severity of illness in transfused patients. Noteworthy, we were able to discriminate the adverse events that occurred after transfusion from those already present prior to the transfusion to avoid protopathic bias, or lagging, which is rarely taken into account in similar observational studies. It is impossible to conclude however, with a prospective study design, whether the adverse outcome was associated with the exposure or the patients' baseline characteristics. In any case, a randomized trial of different transfusion strategies in trauma cases would be necessary to conclude on the adverse events associated with RBC transfusion in this group.

A limitation of the current study is the lack of information with respect to mechanism of injury, type of trauma (blunt or penetrating), bleeding sites, organ involvement and types of

emergency surgery required. Pelvic fractures, penetrating injury, open long bone fractures, splenic lacerations and scalp lacerations can lead to massive blood loss. These factors may also be independent determinants of receiving a transfusion in the PICU as supportive non-operative care, including blood transfusion, is the standard of practice for hepatic, splenic and renal injury in hemodynamically stable children (23-25). Indeed, conservative management has been suggested to reduce blood utilization in this population (32), but before restrictive transfusion strategies are implemented, prospective studies in trauma patients detailing types of injury and ongoing hemodynamic stability are needed.

In addition, the data used for the study dates back to 2005, and may not reflect current transfusion practices as it predates the publication of the TRIPICU study, which supports restrictive transfusion strategies in critically ill children (6). As stated above, it is unclear whether transfusion practices have changed significantly in the last few years. Surgical and acute care pediatric subspecialties (orthopedics, general surgery, general pediatrics, PICU) continue to transfusion at a higher Hb trigger than recommended by a restrictive strategy (31), and this study allows us to establish a baseline transfusion trigger and determinants in severe pediatric trauma.

Another possible limitation is the study only included patients admitted to the PICU for over 48h, which represents about 20% of the PICU population. Therefore, there may be a selection bias for more severe and unstable trauma patients. Small sample size prohibited calculation of interaction in multiple regression analysis.

In summary, our study is an important step in the understanding of transfusion practices in pediatric trauma patients. As we move toward a culture of harm reduction in transfusion practice through restrictive transfusion protocols, it remains important to ensure that certain

groups, such as trauma patients, are not at increased risk. Trauma patients admitted to the PICU are at high risk for receiving a RBC transfusion both prior and during their PICU stay. The risks associated with RBC transfusion must be balanced with the risk of hemorrhagic shock and anemia in trauma. A reliable knowledge of RBC transfusion practices in pediatric trauma cases is critical in the preparation of future interventional trials, as transfusion thresholds in this group have not been established, and increasing literature indicates harmful outcomes related to RBC transfusions. Randomized controlled trials are required to determine what would be the optimal RBC transfusion practice in severe pediatric trauma.

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TABLES AND FIGURES

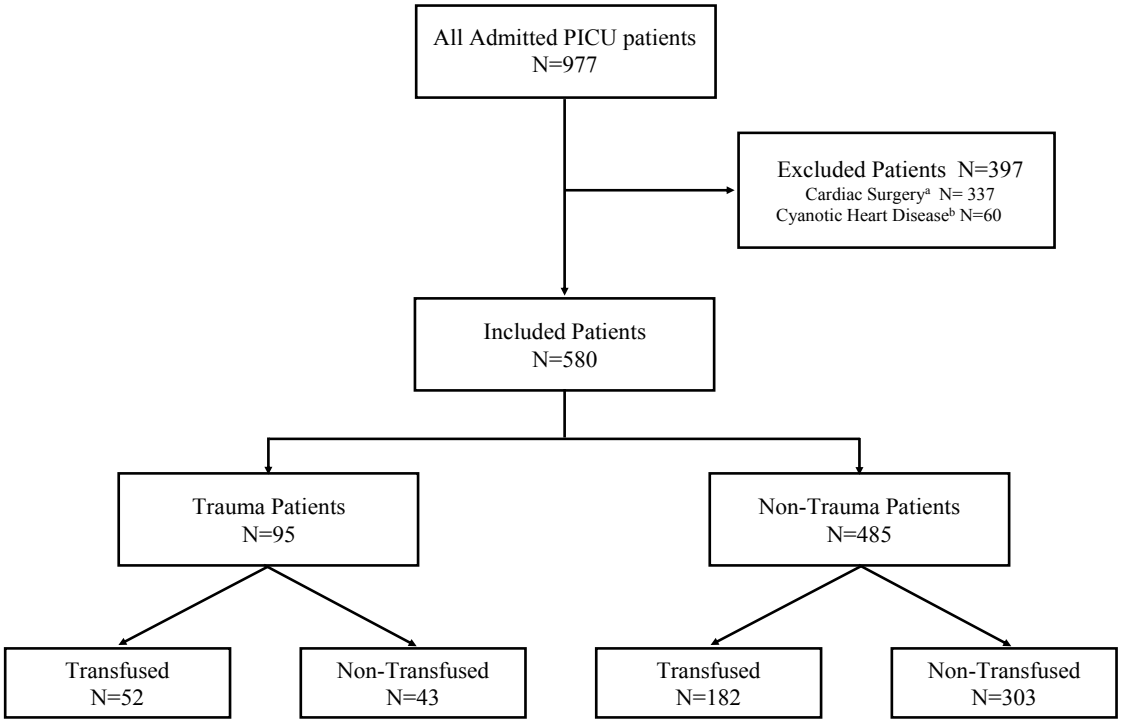


Figure 1A. Flowchart of Patients included in study

a. Includes patients admitted to critical care unit for elective or emergency cardiac surgery not related to trauma
b. Includes all patients with cyanotic heart disease not admitted for cardiac surgery

(* 1 patient labeled at admission for Trauma, + Emergency Cardiac Surgery + Cyanosis was excluded)

Table 1A. Baseline Characteristics at PICU admission of all included patients, and in trauma and non-trauma patients

	All patients (n=580)	Trauma (n=95)	Non-Trauma (n=485)	p- value
Gender, male n (%)	341 (59)	63 (66)	278 (57)	0.11
Age, years mean (SD)	6.7 (±6)	10.15 (±5)	6 (±6)	<0.0001
Weight, kg mean (SD)	28 (±26)	47 (±27)	25 (±24)	<0.0001
PRISM III score[a], median (IQR)	2.0 (0-6)	2.0 (0-7)	2.0 (0-6)	0.41
PELOD score[a], median (IQR)	10 (0-20)	11 (0-20)	10 (0-12)	0.12
Admission Type, n (%)				
Medical	443 (76)	0 (0)	443 (91)	-
Surgical	42 (7)	0(0)	42 (9)	-
Trauma	95 (16)	95 (100)	0 (0)	-
Mechanical ventilation, n (%)	282 (49)	55(58)	227 (47)[c]	0.05
Concomitant shock, n (%)				
Septic shock	59 (10)	0 (0)	59 (12)	< 0.0001
Hemorrhagic shock	9 (2)	7 (7)	2 (0.1)	< 0.0001
Cardiogenic shock	14 (2)	1 (1)	13 (3)	0.48
Other	10 (2)	0 (0)	10 (2)	0.38
None	488 (84)	87 (92)	401 (83)	0.03
Vasoactive agents, n (%)	21 (4)	3 (3)	18 (4)	0.79
Transfusion prior to admission[b]n(%)	57 (10)	20(21)	37(8)[d]	<0.0001
PICU admission hemoglobin, g/dL	N=368	N=72	N=296	
Mean (±SD)	11.2 (±2.4)	11.3 (±2.2)	11.1 (±2.2)	0.86
Transfusion during PICU stay, n(%)	234 (40)	52 (55)	182 (38)	0.0017
Pre-Transfusion hemoglobin, g/dL	N=222	N=47	N=175	
Mean (±SD)	8.4 (±2.4)	9.0 (±2.4)	8.3 (±2.4)	0.090

a. Severity scores of Illness, PRISM III = Pediatric Risk of Mortality Score, PELOD= Pediatric Logistic Organ Dysfunction
b. Within 7 days prior to PICU admission
c. n =484
d. n= 476

Table 2A. Characteristics of Transfused and Non-Transfused Trauma patients

	Trauma (n=95)	Transfused (n=52)	Non-Transfused (n=43)	p-value
Gender male, n (%)	63 (66)	32 (62)	31 (72)	0.38
Age years, mean (±SD)	10.2 (±5.7)	9.0 (±5)	11.5 (±5.6)	0.02
Weight kg, mean (±SD)	47.4 (±28)	43.2 (±27)	52.5 (±28)	0.13
PRISM III[a] score day 1, median (IQR)	2.0 (0-7)	4.5 (0-7)	2.0 (0-5)	0.17
PELOD[a] score day 1, median (IQR)	11 (0-20)	11 (10-21)	10 (0-20)	0.03
Mechanical ventilation[b], n (%)	55 (53)	35 (67)	20 (46)	0.04
Concomitant shock, n(%)	8 (8.5)	8 (15)	0 (0)	0.03
Active bleeding[c], n (%)	22 (23)	16 (31)	6 (14)	0.053
Transfusion prior to admission n(%)[d]	20 (21)	19 (36)	1 (2)	<0.0001
PICU admission hemoglobin (Hb) g/dL	N=72	N=46	N=26	
Mean (±SD)	11.3 (±2.2)	11.0 (±2.5)	11.8 (±1.6)	0.09
Pre-transfusion Hb, or lowest Hb for non-transfused, g/dL, mean (±SD)	N/A	9.0 (±2.4)	9.8 (±2.2)	0.10
Pre-Transfusion Hematocrit, or Lowest in Non-Transfused, %, mean (±SD)	N/A	31.9 (7)	34 (4.5)	0.16

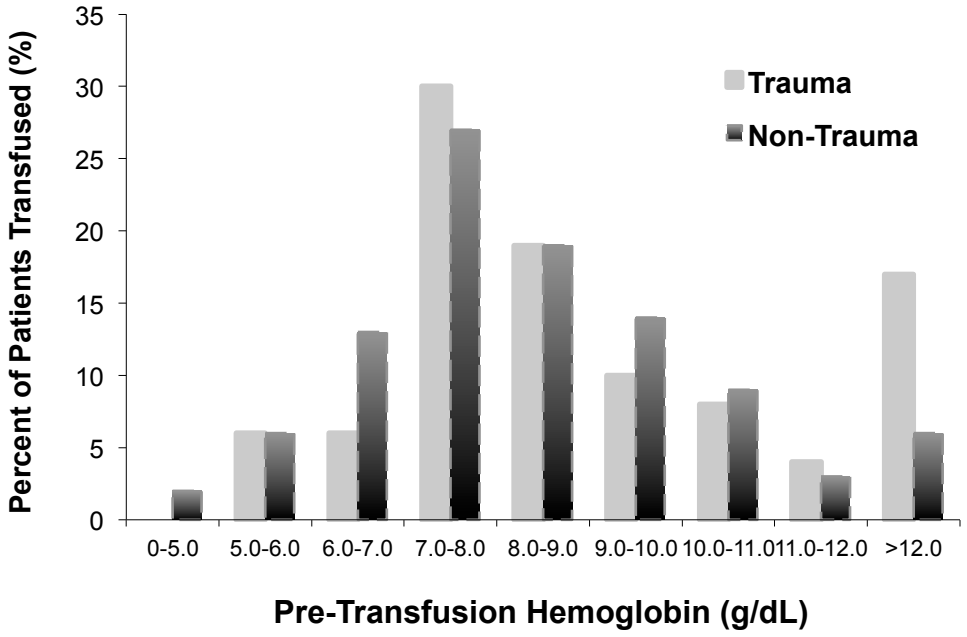
a. Severity scores of Illness, PRISM III = Pediatric Risk of Mortality Score, PELOD= Pediatric Logistic Organ Dysfunction
b. occurring prior to transfusion in transfused patients, or during ICU admission in non –transfused patients
c. includes GI bleeding, chest tubes and drains, other sources
d. Within 7 days prior to admission

Table 3A. Odds Ratios for association of various factors, and red blood cell transfusion in trauma patients*

Predictors of Red Cell Transfusion	**Odds Ratio (95% CI)**	**Chi square P-value**
Age		
0-5 years	Reference	
5-12 years	0.55 (0.13-2.11)	0.39
12-18 years	0.32 (0.10-1.01)	0.052
PELOD 1 score		
0-10	Reference	
≥11	0.95 (0.34-2.67)	0.92
Pre-transfusion or lowest Hb		
	0.76 (0.58-1.00)	0.053
Presence of active Bbleeding		
No	Reference	
Yes	3.13 (0.81-12.19)	0.10
Transfusion prior to PICU		
No	Reference	
Yes	20.36 (2.45-168.7)	0.005

*Odds ratio (OR) calculated using multivariable logistic regression analysis. An OR > 1 represents a greater likelihood for transfusion. All variables included in regression model are presented.

Figure 2A. PICU pre-transfusion hemoglobin levels (in proportions) for trauma and non-trauma patients.



N= 47/52 for Trauma patients, N=175/182 for non-trauma patients, p= 0.09

Table 4A. Characteristics of Blood Transfusions amongst Trauma Patients (N=52)

Characteristics of Patients Transfused	N=52
Transfused cases, n (% of all trauma patients)	52 (54)
Incidence rate of transfusion (transfusion events/1case trauma)	1.5
Volume of Blood during first PICU transfusion (ml/kg), median (IQR)[a]	10 (5-15)
Time from entry to first transfusion (days), n(%)	
Day 1	30 (58)
Day 2	8 (15)
Day 3	6 (11)
Day 4	4 (8)
After Day 5	4 (8)
Number of patients who received 1 transfusion in PICU	21 (40)
Number of patients who received 2 transfusions in PICU	13 (25)
Number of patients who received 3 transfusions in PICU	1 (2)
Number of patients who received 4 transfusions in PICU	9 (17)
Number of patients who received >5 transfusions in PICU	8 (15)
Characteristics of Blood Transfusions received	N = 141
Length of storage of packed RBC in days, median (IQR)[b]	14 (9-21)
Irradiated blood n(%)	8 (25)
Transfusion received n(%)	
Autologous	0 (0)
Related donor	2 (6)
Unrelated donor	29 (94)
Leucocyte depleted n(%)	28 (87)

a: patient values available N=47

b: transfusion values available N=84

Table 5A. Stated Primary and Secondary reasons for giving first transfusion in Trauma patients (n=52) and Non-Trauma patients (n=182).

Primary Reasons for Transfusion, n (%)	Trauma n=52	Non-Trauma n=182
Low hemoglobin	23 (44)	72 (39)
Emergency surgery	3 (9)	1 (0.5)
Acute blood loss	2 (6)	4 (2)
Trauma	2 (6)	0 (0)
Hypotension	1 (3)	1 (0.5)
Elective surgery	1 (3)	1 (0.5)
Extra corporeal membrane oxygenation (ECMO)	0 (0)	7 (4)
Increase oxygen delivery	0 (0)	12 (7)
Other[a]	0 (0)	48 (26)
Reason not stated	20 (38)	36 (20)

[a]includes: cardiovascular dysfunction, tachycardia, symptomatic anemia, exchange transfusion, hemodialysis, shock, hemolysis, apnea, Pre-op and many others.

Table 6A. Incidence rate of outcomes after first transfusion in transfused trauma patients, and during PICU stay in Non-Transfused Trauma patients, (N=95)

Outcome	**Transfused (N=56)**		**Non-Transfused (N=43)**
	Prior to 1st Transfusion	Post 1st Transfusion[a]	Entire PICU stay
Complications, n (%)			
Respiratory dysfunction	6 (11)	9(16)	6 (14)
Reintubation	2 (4)	7 (13)	3 (7)
Fluid overload (CVP >8mmHg)	8 (15)	8 (15)	3 (7)
Cardiovascular dysfunction	5 (10)	8 (15)	2 (5)
Systemic inflammatory response	10 (19)	13 (25)	7 (16)
Hematologic dysfunction	0 (0)	3 (6)	1 (2)
Acute non-hemolytic fever	11 (21)	13 (25)	7 (16)
Nosocomial infection[b]	14 (27)	5 (10)	13 (30)
Neurologic dysfunction	9 (17)	11 (21)	5 (12)
Length of stay in days, mean (SD)	10.8 (7.2)		5.1 (3.8)
Mortality, n (%)	0 (0)		0 (0)

a Occurring during or within first 48h after transfusion in transfused patients
b Includes Catheter related infection, Nosocomial pneumonia, sinusitis and UTI, as well as "other" nosocomial infection.

CHAPTER 7. DISCUSSION

7.1 DISCUSSION AND CHALLENGES ENCOUNTERED IN OSMOTHERAPY STUDY

The paucity of literature for osmolar agents in pediatric TBI created a good starting ground from which this study arose. In order to establish the practices in our center, and practices in TBI, this retrospective study was undertaken. Understanding the clinical issues surrounding the administration of hyperosmolar agents was crucial to prepare for future studies, and attempting to quantify their effect on ICP has rarely been evaluated in pediatrics. We sought to describe practice, reasons for the choice of osmolar agent, and mostly to evaluate the effect of both mannitol and hypertonic 3% saline on ICP.

7.1.1 SAMPLE SIZE

In terms of practice description, the study confirmed that neuromonitoring is not consistently undertaken in pediatric severe TBI. The number of patients meeting eligibility for the study was below what we had initially predicted. We can be thankful for public health promotion reducing the number of deaths associated with motor vehicle accidents in children, and the number of unrestrained passengers; however, a major limitation was the number of severe TBI patients and consequently the number with an ICP monitor. Our first study (not discussed above) attempted to address the reasons for low ICP monitoring rates in severe TBI. It revealed that many severe TBI patients either have an improving GCS score, or a moribund status, both of which can preclude ICP monitoring (18) (see Appendix 1). Once an ICP monitor was placed in the persistently comatose child, hyperosmolar agents were then often given.

The lower rate of ICP monitoring in our center is in line with previous literature on low rates of ICP monitoring in pediatrics (15-17, 45), with the neonatal and infant group being less

frequently neuromonitored. This highlights that our practice is likely similar to other large pediatric centers, supporting its external validity.

Challenges in achieving adequate sample size may then affect the possibilities of statistical analysis that one can conduct. We were unable to compare the effect on ICP of boluses of mannitol versus 3% hypertonic saline between each other, although this was not set as the primary outcome. When a small subset of patients is analyzed over multiple years, the effect of changes in clinical practice and choice of agents may confound results. Furthermore, co-interventions affecting ICP have more important statistical weight when using small sample sizes, and a positive effects is then difficult to detect.

7.1.2 Standardizing practice

The lack of a standardized protocol for sedation and escalation of therapy was another barrier that will need to be addressed prior to prospective studies. Sedation regimens (agents and doses) varied greatly from one patient to another, and there was no specific threshold ICP for administering a hyperosmolar agent, or escalation protocol for uncontrolled ICP. This resulted in agents being given systematically, or without intracranial hypertension (ICP <20mmHh). Patients therefore were difficultly comparable at baseline. There was possibly a decreased effect size related to this inter-subject variability.

Mannitol was less frequently administered than hypertonic saline, making the group size quite small. The lack of adequate sample size made comparison of the 2 groups (mannitol and hypertonic saline) impossible, and the mean difference between groups would have been inaccurate. Larger group size and more frequent data points post bolus would increase the power need to compare the 2 agents. We did not identify any specific factors for the choice of one agent versus the other. Low admission sodium did not appear to dictate choice of hyperosmolar

agent, and the higher rate of 3% hypertonic saline used as first hyperosmolar agent may reflect level II guideline recommendations in pediatrics, although this cannot be validated.

7.1.3 Frequency of Co-interventions

One of the challenges during the study was the frequency of co-interventions to decrease ICP, which were administered post bolus. Intending to monitor ICP for 4h post bolus, we ran into frequent co-interventions (repeated hyperosmolar agents, propofol, intermittent sedation, barbiturates). The period following administration of hyperosmolar agents was therefore frequently contaminated with interventions to reduce the ICP, and future studies will need to take this into account. The possible confounders associated with these co-interventions will therefore affect the internal validity of the study. We considered censoring all data points occurring after a co-intervention, however the small sample size did not permit this type of analysis and conclusions would have been invalid. As mentioned previously, a standardized protocol for escalation of sedation and management of high ICP will also address this challenge.

7.1.4 Future directions in pediatric osmotherapy

Regardless of an increase in sample size, there are inherent biases to retrospective and observational studies where only simple associations can be made. Indeed, in order to truly address the effect of both mannitol and hypertonic saline on a reduction of intracranial pressure, and the superior agent amongst the two, a randomized controlled trial is necessary. A recent study by Shein et al, was the first to prospectively report pharmacotherapeutic ICP reduction in children with severe TBI (46). After co-variate adjustment, they found that hypertonic saline (3%) and phenobarbital were associated with ICP reduction. Given the small number of eligible patients in individual centers, a multicenter, perhaps even international, trial would be warranted. A minimum of about 20 patients per group (40 patients in total) would likely be

necessary to detect a change in ICP post bolus. To control for both within center and amongst center variation in practice and care, a standardized protocol for the management of severe TBI patients would be necessary including; criteria for invasive ICP monitoring, serial data collection, invasive arterial monitoring, temperature and position control, standardized ventilation, protocolized sedation, specific criteria for administration of a hyperosmolar agent and scheduled blood sampling. A standardized management protocol based on guidelines would support the external validity of such a trial.

As a project for an MSc course on randomized trials, I drafted a protocol for a future pilot RCT with a colleague entitled; « HyperOsmolar Therapy for Pediatric Traumatic Brain Injury : The HOT PEaBRain Trial ». The full protocol is available in appendix 4. The study would be a multicenter, randomized, double blind, controlled superiority trial comparing equiosmolar doses of 20% mannitol and 3% saline in the reduction in intracranial pressure. Primary outcomes would be a change in ICP following either of the two agents, and secondary outcomes would be hypotension, hypernatremia, acute renal failure and co-interventions to control ICP. The minimal sample size needed to observe a 20% difference in the change in ICP, with a power of 90% and alpha of 0,05, would be 34 patients. A reduction in ICP between 15 and 20% is what previous studies have used when evaluating effect of hyperosmolar agents on ICP (26, 28). Normalization of ICP could also be used but this would confer more heterogeneity as the starting ICP is much higher for some patients than others. This would be a first trial to detect change in ICP level with hyperosmolar agents, but a much larger randomized -controlled trial (RCT) would be needed to detected a change in the clinical outcomes related to osmotherapy.

7.2 Discussion and challenges in Transfusion in Trauma study

7.2.1 Data subset: Strengths & Limitations

The data used for this study on RBC transfusion practices in pediatric trauma patients admitted to the PICU was very high quality, prospectively collected and included a large sample size of patients from many institutions. Blood loss, blood draws, interventions and transfusions were all very well documented, along with all serial laboratory values related to transfusion. The data subset however, is now 10 years old.

We demonstrated that transfusion in trauma patients was related to younger age, higher PELOD score, mechanical ventilation, and mostly to receiving a blood transfusion prior to admission to the PICU. Interestingly, the pre-transfusion hemoglobin level in trauma and non-trauma patients did not differ significantly, suggesting the adoption of an already restrictive transfusion strategy, or that they bleed rapidly requiring transfusion.

One of the major drawbacks in this study was the age of the data (2005). It is unclear whether transfusion practices have changed over the last decade, but certainly the findings of non-inferiority in the 2007 TRIPICU study had a major impact on transfusion thresholds in pediatrics (38, 39). The awareness of the harmful effects of blood transfusions may mean that we are more frequently applying restrictive transfusion thresholds to patients. A recent article by Klaus et al. however, demonstrates that clinical practice continues to transfuse patients above a restrictive transfusion strategy in pediatric academic centers (47). This suggests that transfusion practice is still not totally restrictive.

Another potential limiting factor was that the study was not designed for trauma patients, and therefore important elements about initial traumatic lesions are not included. There was no information in the database on mechanism of injury, organ involvement, blunt or penetrating

injury, and initial resuscitation to further classify which trauma patients may be at increased risk of hemorrhage requiring transfusion.

The database for the study was also difficult to access for someone who quite junior in statistics and programming, but easily is done so with the help of a statistician. Data output was performed by statistician T. Ducruet. Some specific data were not obtained (initial lactate levels, rate of drop of hemoglobin, lowest blood pressure on arrival…) because of barriers in data extraction, or difficult coding. Independent variables therefore were adjusted to obtain related information in order to draw conclusions.

7.2.2. CATEGORIZING RISK BASED ON THE INITIAL STABILITY

Our study determined that trauma patients admitted to the PICU are at high risk for receiving a blood transfusion and to be transfused early. Furthermore, transfusion prior to arrival to the PICU is an independent risk factor for receiving a blood transfusion after PICU admission. This suggests, that those patients that bleed, bleed substantially, requiring ongoing transfusion to maintain stability. Interestingly enough, the admission hemoglobin is the same for both groups (trauma and non-trauma), suggesting that there is necessarily correction of the low hemoglobin prior to admission, despite ongoing bleeding. Therefore, it must be possible to initially identify the risk factors for those with major bleeding and instability to predict which patients will require further blood products, as opposed to those who can be managed conservatively. A retrospective review of pediatric trauma patients conducted by Allen et al. found that hematocrit, GCS, base deficit and increased severity score were associated with receiving a blood transfusion (48). A recent retrospective study of pediatric trauma patients found that children who received a blood transfusion were at higher risk of needing mechanical ventilation and mortality; and this independent of severity of illness (49). Characterizing this

risk, and the severity of those likely to require a transfusion, will be the next step in establishing the feasibility and safety of restriction transfusion in this group.

7.2.3. Future directions in Transfusion in Trauma

To further understand transfusion practices in trauma, a prospective multicenter transfusion trial including pediatric trauma patients is necessary. With a study specifically designed for trauma patients, included immediately at presentation to hospital, one will be able to characterize the clinical features and laboratory parameters associated with transfusion. This type of study is of course difficult to perform, as consent for a severe trauma patient is difficult to obtain given the acuity of the clinical setting. Nonetheless, a prospective trial in trauma patients is warranted in order to eventually consider the necessity for a randomized trial of restrictive transfusion in stable trauma patients.

Furthermore, therapies attempting to control bleeding are also lacking in pediatrics, but would likely be beneficial in the trauma patient. Tranexamic acid has been shown to improve mortality, and death due to bleeding, in adult trauma patients when given early in trauma management (CRASH -2 Trial) (50), but is currently not used as standard of care in pediatrics. Conducting trials of tranexamic acid in the pediatric trauma patient would help identify whether tranexamic acid could be beneficial when administered in this population.

Chapter 8. Lessons Learned during my MSc

8.1 Feasibility

If I had one thing to tell a future potential MSc candidate, I would say: “Think small, not big”. It seems somewhat contradictory, as it is the exact opposite message I tell my three year old when I say; “You can do and be anything”. It is in fact true though for research, and the

completion of an MSc. I have learned that projects must be feasible, and in a timely manner, in order to produce quality results and maintain the desire to pursue research. One must learn about drafting a protocol, ethics approval, data collection, analysis, re-analysis, article drafting, and literature review all in a very short time. If data collection is too tedious, or statistical analysis to impossible for a junior, then one can get rapidly discouraged, and completion may be quite delayed. I was lucky enough to produce three articles from my MSc research due to excellent supervision, an existing data set in one case, statistical aid from my research department, and a tight schedule to complete given tasks.

8.2 Data collection

Once must have gone through the tedious hours of data collection and entry to comprehend the length, the coding of variables, the difficulty in deciphering charts, and the importance of knowing what non-superfluous information to gather. Realizing that information in charts may be incomplete or missing, or is often very difficult to retrieve, can compromise the internal validity of the study. Furthermore, it is an exercise in patience that researchers must endure and hope to pass off to more junior collaborators over time.

Furthermore, the importance of a sound research question with specific outcome variables is crucial in the creation of a database, so as not to return into charts for a second or third time to gather additional information not initially considered. In addition, not having direct access to the data, and data collection process, may prove to be a further challenge.

8.3. Statistical challenges

One should know how to perform some basic statistics. I learned this too late I believe, and needed to be coached in the end. I was spoiled with the extraordinary help of a statistician on my project on transfusion, and this did not properly equip me initially. Courses in statistics

and hours on the computer with data cleaning clarified the importance of this skill in completing my projects.

8.4. The importance of Supervision

The importance of adequate supervision during research training cannot be stressed enough. As a resident/clinician in clinical research, time is often divided between clinical responsibilities, call, administrative duties, course work and, if one has time, eventually some personal life. Access to timely feedback and responses to research questions are crucial to be able to progress within research. If a question is left answered about methods, data extraction, what statistical test to use, the entire project can be significantly delayed. One needs supervisor availability to provide structured feedback, support, and timely responses to research questions.

8.5 Directions for the Future

Both my clinical work and research projects have incited me to pursue research. I have become acutely aware of the lack of literature and evidence for much of the medical care we provide, and remain interested in care that reduces patient morbidity. In fact, I have developed a passion the maintenance of patient safety standards. With this in mind, the next step in my medical and research endeavors is a PhD in Clinical Epidemiology at the University of Toronto, to which I have already been accepted upon completion of this MSc. My future projects will focus on the epidemiology and the harm related to medication errors in the PICU. I do intend to continue working on improving the literature and the care for trauma patients; both in future TBI protocols for pediatrics and transfusion practices.

CHAPTER 9. CONCLUSION

It is clear that further research is required for the medical care of pediatric trauma patients. In terms of the management of raised intracranial pressure for severe pediatric traumatic brain injury, we can conclude that the use of hyperosmolar therapy is frequent, but choice of agent is not clearly defined, and neither mannitol nor hypertonic saline has clearly been demonstrated to be effective in reducing ICP in this population. Co-interventions to treat high ICP are multiple, and standardized protocols for care are needed for future prospective studies. Many questions are therefore left unanswered, such as whether these agents are effective, for how long, and in which clinical population and setting are they best used. This study has clarified some of the barriers to overcome, and allowed us to outline a prospective trial.

For the management of acute hemorrhage in the trauma patient, we can conclude that red blood cell transfusion are frequent before and after PICU admission, and that initial requirement of a blood transfusion precludes further transfusion despite similar pre-transfusion hemoglobin with non-trauma patients. A prospective trial of restrictive transfusion strategy is warranted in this population. It remains unclear whether trauma patients admitted to the PICU should be candidates for a restrictive transfusion strategy however, and whether this may put them at increased risk for hemorrhagic shock.

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ADDITIONAL FIGURES

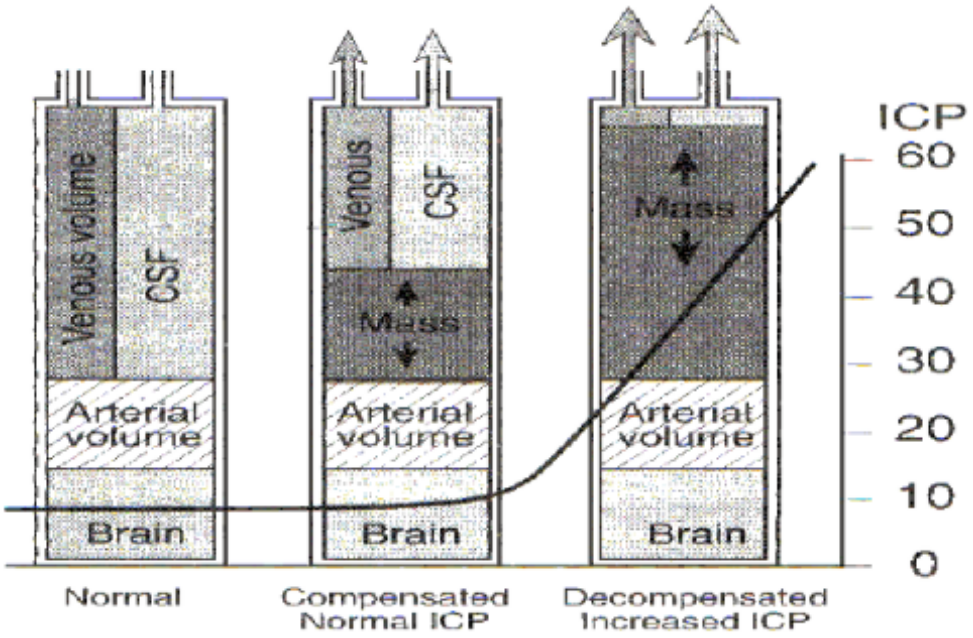
Figure 4. Modified Pediatric Glasgow Coma Score.

PEDIATRIC GLASGOW COMA SCALE (PGCS)				
	> 1 Year		**< 1 Year**	**Score**
EYE OPENING	Spontaneously		Spontaneously	4
	To verbal command		To shout	3
	To pain		To pain	2
	No response		No response	1
MOTOR RESPONSE	Obeys		Spontaneous	6
	Localizes pain		Localizes pain	5
	Flexion-withdrawal		Flexion-withdrawal	4
	Flexion-abnormal (decorticate rigidity)		Flexion-abnormal (decorticate rigidity)	3
	Extension (decerebrate rigidity)		Extension (decerebrate rigidity)	2
	No response		No response	1
	> 5 Years	**2-5 Years**	**0-23 months**	
VERBAL RESPONSE	Oriented	Appropriate words/phrases	Smiles/coos appropriately	5
	Disoriented/confused	Inappropriate words	Cries and is consolable	4
	Inappropriate words	Persistent cries and screams	Persistent inappropriate crying and/or screaming	3
	Incomprehensible sounds	Grunts	Grunts, agitated, and restless	2
	No response	No response	No response	1
TOTAL PEDIATRIC GLASGOW COMA SCORE (3-15):				

Glasgow coma Score (GCS) and modified Glasgow coma score for pediatrics < 5 years.

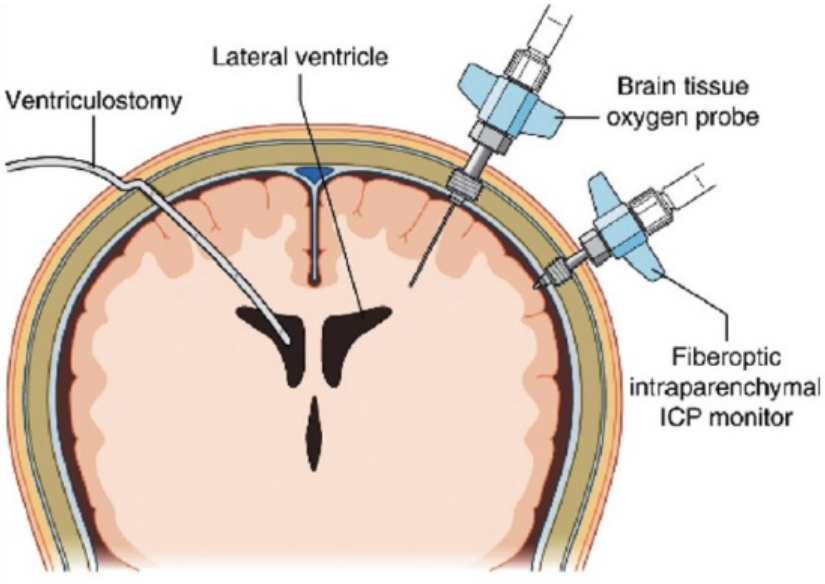
From boneandspine.com

Figure 5. Monroe-Kellie Principle



Source: Rogers (2006) Textbook of Pediatric Intensive Care

Figure 6. Intracranial Pressure Monitoring systems



Source: Fauci AS. Harrison's textbook of Internal Medicine, 17th Edition. http://www.acessmedicine.com

APPENDICES

Appendix 1.

Article

ICP monitoring in children: why we not adhering to guidelines?

Nadia Roumeliotis, Géraldine Pettersen, Louis Crevier , Guillaume Emeriaud.

Childs Nervous System.

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Childs Nerv Syst
DOI 10.1007/s00381-015-2837-9

BRIEF COMMUNICATION

ICP monitoring in children: why are we not adhering to guidelines?

Nadia Roumeliotis[1] · **Géraldine Pettersen**[1] · **Louis Crevier**[2] · **Guillaume Émeriaud**[1]

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Abstract
Background Despite pediatric guidelines, variability exists in the management of severe traumatic brain injury (TBI), as somewhere between 7 and 60 % of children undergo intracranial pressure (ICP) monitoring. Reasons for this low adherence to TBI management guidelines remain unclear. The objective of this study was to evaluate the current practices at CHU Sainte-Justine with regards to ICP monitoring in severe TBI and explore the reasons why ICP monitoring is not undertaken.
Methods A retrospective review was conducted of all patients age 1 month to 18 years, with severe TBI (Glasgow Coma Scale (GCS) ≤8) from 2007 to 2014. Presence of ICP monitoring, head imaging reports, and reasons for lack of monitoring were recorded.
Results Sixty-four patients with severe TBI were admitted. Twenty (31 %) patients had invasive ICP monitoring in the first 6 h and 5 in the following 24 h. Improvement of the GCS on arrival to tertiary care center (20 %, $n=13$) and moribund status (20 %, $n=13$) were the two main reasons ICP monitoring was not undertaken. Fourteen patients (21 %) with reassuring cerebral tomography (Rotterdam scores 1–3) and median GCS 7 (IQR 6–8) were initially followed with clinical surveillance, five of which ended up with an ICP monitor (>6 h).
Conclusion Our study confirms that many children with severe TBI do not undergo ICP monitoring, mainly due to rapid improvement or moribund status. A subgroup of patients, with reassuring cerebral CT scan, was not monitored. Further research is necessary to assess if imaging should be considered in ICP indication, as in adult guidelines.

Keywords Traumatic brain injury · Pediatric · Intracranial pressure monitoring · Practice guidelines · Glasgow coma score

Introduction

Trauma is one of the leading causes of death in children aged 1 to 18 years [1]. Ten percent of traumatic brain injury (TBI) is considered severe [2], defined as an initial Glasgow Coma Scale (GCS) ≤8, with high morbidity and mortality [3, 4]. Current adult and pediatric guidelines for the management of severe TBI suggest that patients should undergo invasive intracranial pressure (ICP) monitoring, despite a lack of grade 1 evidence [5, 6]. Literature, however, reports considerable variability in the use of ICP monitoring in children, with particularly low rates in infants and toddlers [7, 8]. A large prospective UK database found that 59 % of children with severe TBI underwent ICP monitoring [7], whereas queries of the United States National Trauma Data Bank found rates of 8 % [9] and 27 % [10], respectively. These studies lack the details with regards to why ICP monitoring is not undertaken. To date, no studies have investigated the reasons for lack of ICP monitoring in children.

The objective of this study was to evaluate our current practices with regards to ICP monitoring and explore the reasons for which monitoring was not undertaken.

[1] Department of Critical Care, Sainte-Justine Hospital, University of Montréal, 3175 Cote Sainte-Catherine, Montréal, Québec, Canada H3T 1C5

[2] Department of Neurosurgery, Sainte-Justine Hospital, University of Montréal, 3175 Cote Sainte-Catherine, Montréal, Québec, Canada H3T 1C5

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Table 1 Baseline characteristics of patients

	All patients, *N*=64	ICP monitor, *N*=25	No ICP monitor, *N*=39
Age (mean years±SD[a])	8.3±5.6	9.7±5.2	7.3±5.8
Patients aged <2 years (no. (%))	12 (19)	2 (8)	10 (26)
Male sex (no. (%))	39 (61)	19 (76)	20 (51)
Mechanism of injury (no. (%))			
Accident auto-pedestrian	9 (14)	3 (12)	7 (18)
Accident auto-bicycle	6 (9)	2 (8)	3 (8)
Accident auto-auto	20 (31)	7 (28)	13 (33)
Accident ATV[b]	2 (3)	1 (4)	1 (3)
Sports injury	2 (3)	1 (4)	1 (3)
Fall	5 (8)	2 (8)	3 (8)
Suspected abuse	9 (14)	2 (8)	7 (18)
Other	11 (17)	7 (28)	4 (10)
Initial GCS (median score (25th–75th percentile))	6 (4–7)	6 (4–7)	6 (4–7)
Pediatric trauma score[c] (median score (25th–75th percentile))	5 (2–7)	5 (3–7)	4 (1–7.5)
Polytrauma (no. (%))	27 (42)	11 (44)	16 (41)
External ventricular drain (no. (%))	2 (3)	2 (8)	0 (0)
Death (no. (%))	19 (30)	6 (24)	13 (33)

[a] Standard Deviation

[b] All Terrain Vehicle

[c] Score range from −6 to +12 with lower score associated with increased mortality

Methods

A retrospective chart review of all consecutive TBI patients admitted to CHU Sainte-Justine between April 2007 and April 2014 was conducted. Patients between 1 month and 18 years of age were included if their GCS after initial stabilization was ≤8. Sainte-Justine Hospital is a university-affiliated tertiary care center in Montreal, Canada, and a reference center for pediatric trauma. Patient demographics, mechanism of injury, and clinical data were obtained from the chart. Placement of ICP monitor in the first 6 h was considered in line with guidelines. Reasons for lack of ICP monitoring were obtained from neurosurgical and intensive care charting. Final head CT reports were reviewed retrospectively for Rotterdam scoring [11]. Although conceived in adults, the score has recently been used for mortality risk stratification in children [12].

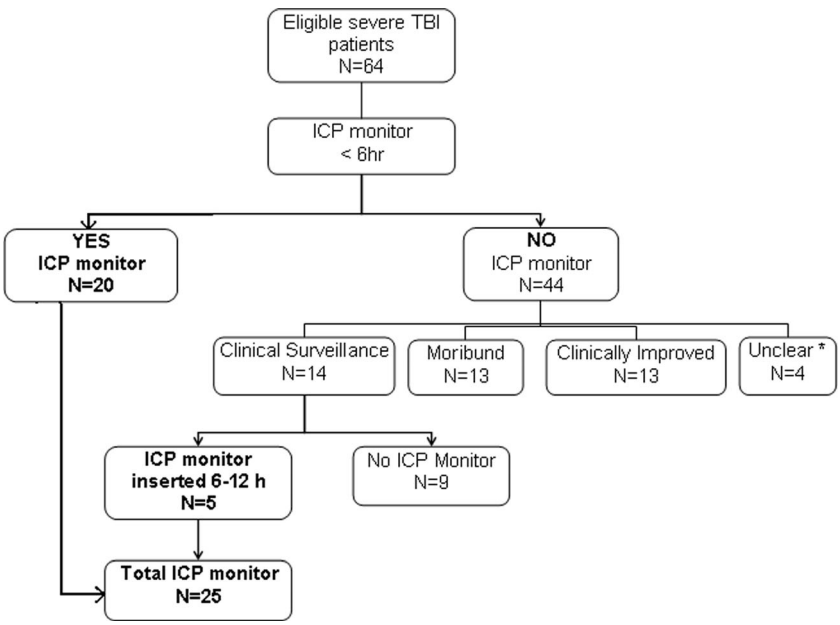

Fig. 1 Flow chart of patients included in study

Table 2 Rotterdam CT imaging score of patients initially managed with clinical surveillance (N=14)

Score, associated mortality 6 month post-injury [12]	Improved, N=9	ICP monitor, N=5
Score 1, 0 %	1	0
Score 2, 7 %	8	2
Score 3, 16 %	0	3
Score 4, 26 %	0	0
Score 5, 53 %	0	0
Score 6, 61 %	0	0

The study was approved by the research ethics board of our institution (#3546) with a waiver of consent.

Results are expressed in proportions and mean or median values, with respective standard deviations (SDs) and interquartile range (25th–75th percentile) when appropriate.

Results

Seventy-six patients with TBI were identified during the study period, and 64 patients with severe TBI met inclusion. Patient demographics are described in Table 1. A description of patient management is described in Fig. 1. Of the 64 patients, 20 (31 %) underwent immediate ICP monitor placement in the first 6 h after arrival to the emergency department. Of the 44 patients (68 %) who did not undergo immediate ICP monitoring, the primary causes were improving GCS on arrival (n=13, 20 %) and moribund status (n=13, 20 %) as well as decision for clinical surveillance (N=14, 22 %). There were four patients for whom it was unclear based on chart data why ICP monitoring was not undertaken. In the patients managed with clinical surveillance (N=14), five eventually underwent ICP monitor placement in the first 24 h (range 7–21 h) and nine clinically improved not requiring invasive monitoring. The Rotterdam CT head scores of those managed with clinical surveillance are presented in Table 2. All of the patients without ICP monitor had a favorable clinical outcome, and one death occurred in a patient with delayed ICP placement (>6 h). A total of 25 patients (39 %) therefore underwent ICP monitor placement of the 64 severe TBI patients. Twenty-five percent of our patients were below 2 years of age, and only 20 % of those (2/10) underwent ICP monitoring.

Discussion

Our study confirms that a minority of pediatric patients with criteria for ICP monitoring actually undergoes monitoring. Guidelines for the management of pediatric TBI [6] suggest placement of an ICP monitor for severe TBI, despite a lack of evidence. Our study is comparable to previous studies in pediatrics and confirms low use of ICP monitoring in children. This is the first study to explore the reasons for lack of ICP monitoring in the pediatric population. Our results suggest that there may frequently be a clinical justification for low rates of ICP placement. The decision not to monitor ICP often weighs clinical risks and benefits; it is perhaps too invasive and risky in patients with improving GCS and is futile in moribund patients with catastrophic brain injury. The challenge relies in the clinical judgment of assessing patients whose clinical assessment at the time of presentation warrants ICP monitoring. Failure to monitor ICP may have adverse neurological impacts; however, blindly applying protocol may result in unnecessary risks in many patients.

Head imaging likely influences the decision to place an ICP monitor. Recent pediatric model taking into account GCS, Rotterdam score, mechanism of injury, and severity score proved to be accurate for prediction mortality risk stratification in pediatrics [12]. Our results support the link between GCS, reassuring tomography score and decision not to undergo ICP monitoring. Although the observational design of the study prevents us from evaluating the accurateness of this practice, we speculate that this seems reasonable, given adult guidelines which take head imaging into account in their management algorithms [5].

Of the patients who underwent ICP monitoring, five had their monitors placed over 6 h after their arrival to the emergency department, suggesting that they were initially managed with clinical surveillance and failed to improve, requiring the placement of an ICP monitor. This underlines the need for continual clinical reassessment of the severely brain-injured patient but also highlights the possible risks associated with delayed ICP placement. We can hypothesize that the patients who were managed with clinical surveillance and never underwent ICP monitoring, likely would not have benefited from monitoring, as all had a favorable outcome.

Greater standardization is needed in the management of children with severe TBI, and efforts should be made to better understand why practice varies. This study suggests that reassuring head CT and stable clinical exam frequently leads to clinical surveillance in our center, with no evident adverse event. Further research is needed to ascertain if imaging could safely be considered in the guidelines and management of these patients.

Conflict of interest All authors have no conflicts of interest to report.

Ethical standard statement Study was conducted with ethics board approval and met highest ethical standards.

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Appendix 2.

Article

Anemia, blood loss, and blood transfusions in North American children in the intensive care unit.

Bateman ST, Lacroix J, Boven K, Forbes P, Barton R, Thomas NJ, Jacobs B, Markovitz B, Goldstein B, Hanson JH, Li HA, Randolph AG; Pediatric Acute Lung Injury and Sepsis Investigators Network.

Am J Respir Crit Care Med.

2008 Jul 1;178(1):26-33.

Anemia, Blood Loss, and Blood Transfusions in North American Children in the Intensive Care Unit

Scot T. Bateman[1], Jacques Lacroix[2], Katia Boven[3], Peter Forbes[4], Roger Barton[5], Neal J. Thomas[6], Brian Jacobs[7], Barry Markovitz[8], Brahm Goldstein[9], James H. Hanson[10], H. Agnes Li[3], and Adrienne G. Randolph[4], for the Pediatric Acute Lung Injury and Sepsis Investigators Network*

[1]University of Massachusetts Medical Center, Worcester, Massachusetts; [2]CHU Sainte-Justine, Montreal, Canada; [3]Johnson and Johnson Pharmaceutical, Research and Development, Raritan, New Jersey; [4]Children's Hospital, Boston, Massachusetts; [5]Children's Hospital of Saint Francis, Tulsa, Oklahoma; [6]Penn State Children's Hospital, Hershey, Pennsylvania; [7]Children's National Medical Center, Washington, DC; [8]Children's Hospital of Los Angeles, Los Angeles, California; [9]Novo Nordisk, Inc., Princeton, New Jersey; and [10]Children's Hospital and Research Center Oakland, Oakland, California

Rationale: **Minimizing exposure of children to blood products is desirable.**

Objectives: **We aimed to understand anemia development, blood loss, and red blood cell (RBC) transfusions in the pediatric intensive care unit (PICU).**

Methods: **Prospective, multicenter, 6-month observational study in 30 PICUs. Data were collected on consecutive children (<18 yr old) in the PICU for 48 hours or more.**

Measurements and Main Results: **Anemia development, blood loss, and RBC transfusions were measured. A total of 977 children were enrolled. Most (74%) children were anemic in the PICU (33% on admission, 41% developed anemia). Blood draws accounted for 73% of daily blood loss; median loss was 5.0 ml/day. Forty-nine percent of children received transfusions; 74% of first transfusions were on Days 1–2. After adjusting for age and illness severity, compared with nontransfused children, children who underwent transfusion had significantly longer days of mechanical ventilation (2.1 d, $P < 0.001$) and PICU stay (1.8 d, $P = 0.03$), and had increased mortality (odds ratio [OR], 11.6; 95% confidence interval [CI], 1.43–90.9; $P = 0.02$), nosocomial infections (OR, 1.9; 95% CI, 1.2–3.0; $P = 0.004$), and cardiorespiratory dysfunction (OR, 2.1; 95% CI, 1.5–3.0; $P < 0.001$). High blood loss per kilogram body weight from blood draws (OR, 1.11; 95% CI, 1.03–1.2; $P = 0.01$) was associated with RBC transfusion more than 48 hours after admission. The most common indication for transfusion was low hemoglobin (42%). Pretransfusion hemoglobin values varied greatly (mean, 9.7 ± 2.7 g/dl).**

Conclusions: **Critically ill children are at significant risk for developing anemia and receiving blood transfusions. Transfusion in the PICU was associated with worse outcomes. It is imperative to minimize blood loss from blood draws and to set clear transfusion thresholds.**

Keywords: blood loss; anemia; transfusions; pediatric; intensive care; red blood cells

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Recent emphasis directed toward minimizing anemia and decreasing transfusions in critically ill adult patients has led to a significant need to better understand the burden of anemia and transfusions in critically ill children.

What This Study Adds to the Field

Critically ill children are at significant risk for developing anemia and receiving blood transfusions. Transfusion in the PICU was associated with worse outcomes.

Anemia is common in critically ill children admitted to the pediatric intensive care unit (PICU) (1). There are numerous possible causes for the anemia of critical illness, including chronic anemia, overt and occult blood loss (2), underlying disease and treatments causing bone marrow suppression. An inadequate erythropoietin response to anemia in critically ill patients is described in adults (3–5) as well as in children (1). However, there are no data available on blood loss in children admitted to the PICU.

Red blood cell (RBC) transfusions are a common therapy in critically ill and injured children. There are multiple risks associated with RBC transfusions, including transfusion-transmitted infections, transfusion-related acute lung injury, hemodynamic compromise, intravascular volume overload, acute hemolysis, and immunosuppression (6–9). In adults, RBC transfusions have also been associated with prolongation of mechanical ventilation (10), diminished organ function, and even death (11, 12). To date, no multicenter prospective data on anemia and transfusions in the PICU are available.

In this study, we focused on children with a longer PICU stay who could most benefit from PICU interventions such as blood conservation protocols or erythropoietin therapy. Children with a PICU stay greater than 48 hours represent approximately 20% of PICU admissions, but account for disproportionately high PICU resource utilization (13). We aimed to prospectively assess the epidemiology of anemia and red cell transfusions in this population as well as to determine the causes of blood loss in the PICU. Outcomes and complications were captured to assess any association with transfusions.

METHODS

This was a prospective, multicenter, epidemiologic, observational study conducted in 30 PICUs of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network in the United States and Canada from September 8, 2004, to March 29, 2005. All consecutive children, younger than 18 years, admitted for any reason were eligible for study enrollment once remaining in the PICU for more than 48 hours (*see* the online

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*A list of participating PALISI investigators appears at the end of this article.

Correspondence and requests for reprints should be addressed to Scot T. Bateman, M.D., University of Massachusetts Medical Center, Department of Pediatrics, H5-524, 55 Lake Avenue, North Worcester, MA 01655. E-mail:

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

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supplement for information on children with PICU stay ⩽ 48 h). Exclusion criteria included the following: premature neonates (corrected gestational age ⩽ 37 wk and age < 28 d), prior participation in the survey, family history of refusing blood transfusions, involvement in other transfusion or blood management–related research, pregnancy, impending brain death, and recent (within 7 d) PICU stay of more than 72 hours. Enrollment in the study continued until the predefined sample size (~1,000 children with length of stay > 48 h) had been reached. The survey did not require additional interventions/procedures that were not part of routine medical practice. The institutional review board approved the study at each site. Written, informed consent was obtained for all enrolled subjects.

All blood loss information was collected prospectively on all children from admission onward. Other data from the first 48 hours after admission were collected retrospectively. All data after 48 hours of admission were collected prospectively. The number of blood draws and volume of each draw were recorded by the bedside nurse and collected for all children each day the patient remained in the PICU. A day was defined as a calendar day starting at midnight. Data were collected for all participants for a maximum of 28 days total or until hospital discharge, interinstitutional transfer, or death. Children readmitted to the PICU less than 48 hours after transfer were regarded as still in the PICU.

Data collected on admission included the following: demographics, severity of illness using the Pediatric Risk of Mortality (PRISM) III score (14), organ dysfunction using Pediatric Logistic Organ Dysfunction (PELOD) score (15), and multiple organ dysfunction score (MODS) (16). Daily data collection included lowest daily hemoglobin (Hb) level, RBC transfusion events, reason for physician ordering transfusion, blood loss from blood draws, PELOD and MODS variables, and clinical events including mechanical ventilation, specific technologies, surgery, or complications. Anemia was defined as an Hb concentration 2 SD below the mean Hb concentration for each age group. The cutoff values to determine anemia were as follows: 14.5 g/dl for neonates, dropping to 9 g/dl at 2 months of age, then rising to 10.5 g/dl at 6 months of age, 11.5 g/dl at 2 years of age, and 12 g/dl in females and 13 g/dl in males at adolescence (17). The following categories of severity of anemia were created for subsequent analysis to assess the impact on degree of anemia: "severe anemia," an Hb of less than 7.0 g/dl; "moderate anemia," an Hb greater than 7.0 and less than 10.0 g/dl; and "mild anemia," anemia and an Hb greater than 10 g/dl.

Chi-square tests were used to make unadjusted bivariate tests of association between the outcomes and categorical predictors. For continuous predictors, Student's *t* tests were used. Children with anemia on admission to the PICU, children who became anemic during their PICU stay, and children who were never anemic were compared with analysis of variance. The relationship between complications and transfusion on Day 1 or 2 was examined by comparing the complications on Day 3 or later in two groups: (*1*) those with one or more transfusions on Day 1 or 2 (n = 363) and (*2*) those with no transfusions during their PICU stay (n = 494). Logistic regression, adjusted for age and admission PRISM III score, was used to compare odds of complication for the subjects who did or did not undergo transfusion. Logistic regression was also used to model risk for developing anemia and risk for receiving a transfusion. Separate regression models were computed for each outcome. In each case, a backward variable selection procedure was used to eliminate predictors not significantly associated with the outcomes. Determination of clinical risk factors for the logistic regression models—(*1*) developing anemia after Day 2 and (*2*) getting a transfusion after Day 2—were calculated. Children receiving extracorporeal membranous oxygenation (ECMO) on Day 1 or 2 (n = 19) were excluded from regression models (SAS version 9.1; SAS Institute, Cary, NC). Median Hb for the transfused and nontransfused groups was compared by ranking Hb levels, by day, for the two transfusion groups combined and using a generalized estimating equations regression model (SAS Proc Genmod; SAS Institute) to test for a main effect of transfusion group.

RESULTS

Children were enrolled from moderate- to large-sized PICUs (70% in children's hospitals and 60% in academic centers) in the United States (25 sites, at least 1 from each U.S. Census region) and Canada (5 sites from 4 regions). Table E1 (*see* the online supplement) details enrollment by census region. The median number of PICU beds was 20 (range, 8–67).

There were 5,570 admissions during the study period; 1,097 (19.7%) remained in the PICU for more than 48 hours. Of these, 986 were enrolled (consent rate, 89.9%). There were nine incomplete case report forms (0.7%) from one study site, leaving 977 children for analysis. Baseline demographic characteristics of these children are presented in Table 1 together with baseline data on anemic children, children who received a transfusion, and those that developed anemia or received a late transfusion.

In the youngest age category (⩽28 d), 63% of patients were primarily admitted as surgical nontrauma, whereas in the three oldest age groups, the highest proportion of children were admitted as medical nontrauma. Children in the age category ranging from 28 days to less than 2 years were equally distributed between these two admission types. The most common primary PICU admitting diagnostic category for children younger than 28 days was the cardiovascular system (n = 62 [75%]). In contrast, the respiratory system was most common among the three middle age categories (38–42% of children). In the oldest age group, the respiratory and central nervous systems were the most common admitting diagnostic categories (32 and 34% of children, respectively). There was an increasing trend with age in the proportion of children whose primary PICU admitting diagnostic category was the central nervous system.

Anemia

A history of anemia within 7 days before PICU admission was reported in 15% of children. Anemia in the PICU was common: it was present on admission in 33% of children. An additional 41% became anemic during their PICU stay. Only 26% of the children never became anemic. Anemia overall (either on admission or during PICU stay) was more common in neonates and adolescents (Figure 1) ($P < 0.0001$).

Children with anemia on admission to the PICU had a higher severity of illness score with higher PRISM III (mean, 5.3 ± 5.8) than children who became anemic during their PICU stay (mean, 3.8 ± 5.1) and children who were never anemic (mean, 3.3 ± 4.5) ($P < 0.0001$). There was no difference in the amount of average daily blood loss from all sources among these three groups. The PICU length of stay was greatest in the group who developed anemia in the PICU (mean, 10.4 ± 7.8 d) compared with those anemic on admission (8.9 ± 7.0 d) or never anemic (6.6 ± 5.9 d) ($P < 0.0001$). In addition, children who developed anemia in the PICU had more days of mechanical ventilation (mean, 6.7 d) than those anemic on admission (5.7 d) or never anemic (2.7 d) ($P < 0.0001$).

A multivariate logistic regression model was used to identify independent risk factors fore children developing anemia more than 48 hours after admission. Children were excluded if they were receiving ECMO or if they had anemia on admission or anemia on Days 1–2 (438 children were left for analysis; 176 developed anemia). Factors predictive of anemia development in the univariate analyses were tested in the multivariate model and are reported in Table 2. Significant predictors of initial anemia development more than 48 hours after PICU admission were age of 28 days or younger, no RBC transfusion on PICU Days 1–2, presence of shock on PICU admission, admission category of "other" (gastrointestinal, endocrine, renal, hematology/oncology), baseline PELOD score of 11 or more, and having a respiratory comorbid condition. Factors not predictive of developing later anemia in the bivariate analysis were transfusion before admission, sex, race, admission type (medical, surgical nontrauma, trauma), PRISM III score (0, 1–5, ⩾6), and blood loss/kg from blood draws on admission for Days 1–2.

TABLE 1. BASELINE CHARACTERISTICS OF THE CHILDREN ON ADMISSION TO THE PEDIATRIC INTENSIVE CARE UNIT

	All Children, n (%) (*n = 977*)	Anemia on Admission, n (%) (*n = 322*)	Develop Anemia >48 h after Admit, n (%) (*n = 176*)	Any Transfusion in PICU, n (%) (*n = 475*)	Transfusion >48 h after Admit, n (%) (*n = 162*)
Age group					
<28 d	83 (8)	28 (9)	23 (13)	58 (12)	26 (16)
⩾28 d to <2 yr	358 (37)	82 (25)	72 (41)	208 (44)	63 (39)
⩾2 yr to <5 yr	137 (14)	38 (12)	28 (16)	57 (12)	19 (12)
⩾5 yr to <12 yr	183 (19)	72 (22)	28 (16)	67 (14)	24 (15)
⩾12 yr to <18 yr	216 (22)	102 (32)	25 (14)	85 (18)	30 (19)
Male sex	575 (59)	203 (63)	102 (58)	276 (58)	88 (54)
Admitting type					
Trauma	99 (10)	50 (16)	11 (6)	56 (12)	15 (9)
Surgical, nontrauma	383 (39)	106 (33)	75 (43)	216 (45)	53 (33)
Medical, nontrauma	495 (51)	166 (52)	90 (51)	203 (43)	94 (58)
Admitting category					
Cardiovascular system	253 (26)	58 (18)	50 (28)	187 (39)	53 (33)
Nervous system	217 (22)	82 (26)	34 (19)	79 (17)	24 (15)
Digestive system	62 (6)	29 (9)	17 (10)	40 (8)	14 (9)
Endocrine system	17 (2)	3 (1)	4 (2)	6 (1)	4 (3)
Hematologic	39 (4)	27 (8)	1 (1)	31 (7)	9 (6)
Renal/urologic	22 (2)	14 (4)	3 (2)	16 (3)	4 (3)
Respiratory	353 (36)	102 (32)	66 (37)	111 (23)	53 (33)
Comorbid conditions*					
None	387 (40)	127 (39)	69 (39)	185 (39)	58 (36)
Asthma	112 (12)	37 (11)	17 (10)	36 (8)	13 (8)
Cyanotic congenital heart disease	136 (14)	25 (8)	34 (19)	110 (23)	33 (20)
Nervous system	199 (20)	65 (20)	38 (22)	66 (14)	27 (17)
Renal and urologic	80 (8)	34 (11)	14 (8)	44 (9)	12 (7)
Other	128 (13)	46 (15)	18 (10)	73 (16)	19 (12)
PRISM III score					
Mean (SD)	4.2 (5.3)	5.3 (5.8)	3.6 (4.5)	5.6 (5.8)	4.5 (5.1)
Median	2.0	4.0	2.0	4.0	3.0

Definition of abbreviations: MODS = multisystem organ dysfunction score; PELOD = Pediatric Logistic Organ Dysfunction; PICU = pediatric intensive care unit; PRISM = Pediatric Risk of Mortality.

* A patient can present with more than one comorbid condition.

Blood Loss

Almost all children (96.5%) had blood loss from blood draws, 325 (33%) had some blood loss due to procedures (median daily loss was 0.25 ml/kg), and 233 (24%) had blood loss due to spontaneous bleeding (median daily loss was 2.56 ml/kg). Blood loss from blood draws accounted for the majority of total blood loss during the ICU stay in all age groups (mean, 72.9%; median, 100%). Children who had either an arterial line or a central venous catheter in place during the PICU stay had a 2.3- to 4-times higher median number of blood draws per day through Day 14 of their PICU stay than children with peripheral venous lines only.

The mean volume of blood loss per blood draw was 2.7 ± 2.3 ml/draw (median, 2.0 ml/draw). There were a mean of three blood draws/day with a mean daily volume of blood loss of 8.25 ± 21.5 ml/day (median, 5.0 ml/d; adjusted for weight, 0.32 ml/kg/d). An analysis of daily blood loss from blood draws by age category adjusted for weight (kg) shows an inverse relationship between blood loss/kg and age ($P = 0.02$) (Figure 2). For all children, there was a decreasing trend in the median number of daily blood draws per patient over time during the PICU stay, with the highest number of blood draws per patient (mean, 7; median, 6) occurring on the second calendar day of admission.

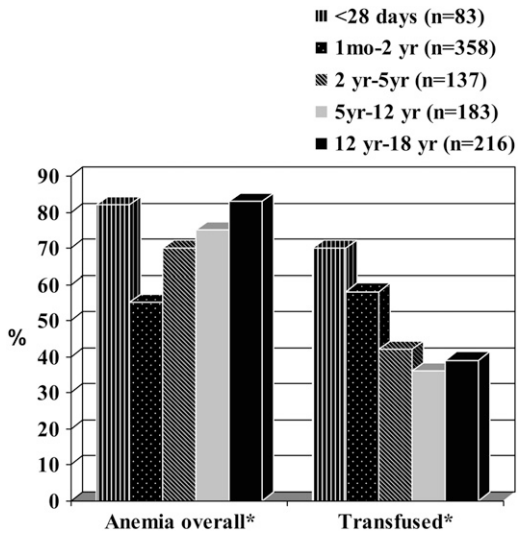

Figure 1. Proportion of patients with anemia overall (patients with anemia on admission coupled with those that developed anemia in the pediatric intensive care unit [PICU]) and of patients who received at least one red blood cell transfusion during their PICU stay. *Groups were statistically different by age ($P < 0.0001$).

RBC Transfusion

Overall, 475 (49%) children received one or more RBC transfusions during the PICU stay and 6% received a transfusion after PICU discharge. The first transfusion was given within 48 hours of PICU admission 74% of the time (22% received their first transfusion between Days 2 and 7, and only 4% received their first transfusion > 7 d after admission to PICU). One hundred eighty-one (38%) children who received a transfusion had only one transfusion, whereas 110 (23%) had two, 50 (11%) had three, and 34 (7%) had four transfusions. The remaining 100 (21%) had four or more transfusions, and this group received 1,017 (50%) of all transfusion events. The time course of transfusions is

TABLE 2. PREDICTORS OF DEVELOPMENT OF ANEMIA AFTER PEDIATRIC INTENSIVE CARE UNIT DAY 2 (n = 438)*

Effect	Odds Ratio (95% Wald confidence limits)	*P* Value
Age category		
<28 d	4.9 (1.8–13.4)	
⩾28 d to <2 yr	0.9 (0.4–1.6)	
⩾2 yr to <5 yr	1.1 (0.5–2.3)	
⩾5 yr to <12 yr	Reference	
⩾12 yr to ⩽18 yr	1.2 (0.5–2.6)	<0.01
Female vs. male	1.1 (0.7–1.6)	0.73
Race		
White	Reference	
Asian	3.3 (0.7–14.4)	
Black	1.4 (0.6–3.0)	
Other	1.1 (0.6–2.0)	0.38
No transfusion ICU Days 1–2	2.6 (1.4–4.8)	<0.01
Absence of shock on admission	0.4 (0.2–1.0)	0.04
Primary admission category		
Respiratory	Reference	
Cardiovascular system	0.7 (0.4–1.3)	
Central nervous system	0.9 (0.5–1.7)	
Other†	4.5 (1.9–10.2)	<0.001
PELOD score		
0	0.5 (0.3–0.9)	
1–10	0.6 (0.3–1.0)	
⩾11	Reference	0.04
Chronic conditions		
Respiratory	1.9	
Nonrespiratory	Reference	0.04

Definition of abbreviation: PELOD = Pediatric Logistic Organ Dysfunction.

* Children on extracorporeal membranous oxygenation Days 1–2, anemic on admission, or anemic on Days 1–2 were excluded (n = 539).

† Other included gastrointestinal, hematology, endocrine, or renal.

presented in Figure 3, which shows the predominance of early transfusions. Transfusion-related complications of fever, hemolysis, or transfusion reaction were rare at 0.5%.

Data on packed RBC (PRBC) characteristics were available for 1,301 transfusions that occurred in the PICU after enrollment. This revealed that 69% of these PICU transfusions were with irradiated blood, 92% were from unrelated donors, and 86% were leukocyte depleted. The storage age of the blood was recorded in 1,288 transfusions. Sixty-five percent (842) of the PRBCs given were less than or equal to 14 days of storage. The mean age of the blood, when recorded, was 13.3 days.

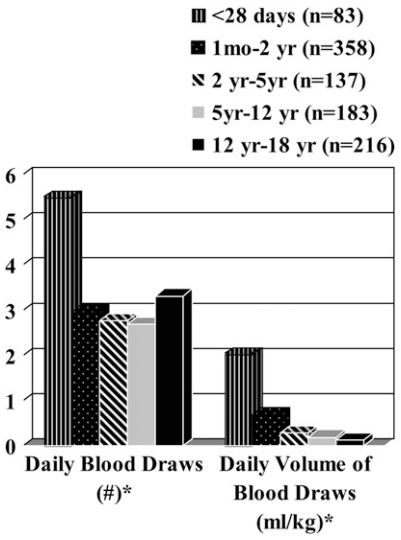

Figure 2. Average number of blood draws per day per patient and average volume of blood collected per day per patient by age of patients. *Groups were statistically different by age ($P <$ 0.02).

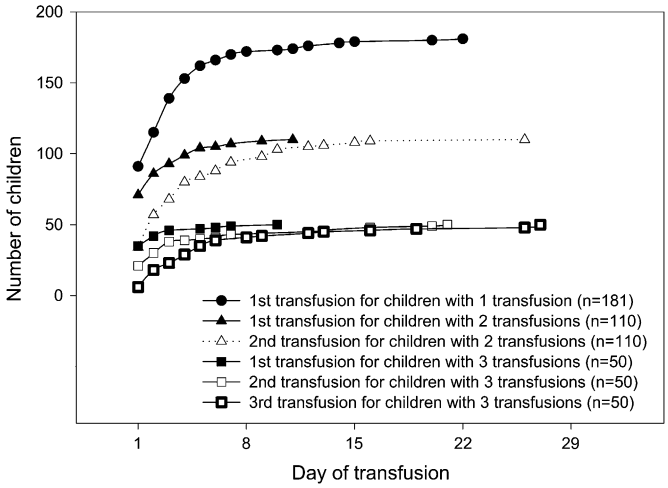

Figure 3. Cumulative distribution of day of transfusion for children with one, two, and three total transfusions.

Compared with the subset of children who did not receive a transfusion during the PICU stay, the children who received a transfusion in the PICU were younger (mean age, 4.5 vs. 6.6 yr; $P < 0.001$), had a higher rate of anemia on admission (44 vs. 22%, $P < 0.001$), and had higher baseline PRISM III score ($P < 0.001$). Transfusion incidence by age is presented in Figure 1. Children who received at least one RBC transfusion during their PICU stay also had a greater average daily blood loss (median, 1.6 vs. 0.2 ml/kg; $P < 0.001$), a higher incidence of anemia (24 vs. 7%, $P <$ 0.001) and transfusions (41 vs. 2%, $P < 0.001$) within 7 days before PICU admission, more surgical/invasive procedures at PICU admission (47 vs. 38%, $P = 0.003$), and more shock on admission (21 vs. 6%, $P < 0.001$). Most of the children who had a primary admitting diagnosis pertaining to the cardiovascular system received a transfusion during the PICU stay (74%).

A total of 3,521 predefined complications were documented during the PICU stay. The effect of transfusion on outcomes was evaluated by comparing PICU complications that occurred after 48 hours in those children who had received a transfusion on Day 1 or 2 (n = 363) with those who never received a transfusion (n = 494) during their PICU stay. Correcting for age and for admitting PRISM III scores, the transfused group had an increased risk of death (odds ratio [OR], 11.6; 95% confidence interval [CI], 1.43–90.9; $P = 0.02$), an increased risk of death and/or cardiac arrest (OR, 20.0; 95% CI, 2.6–166.7; $P =$ 0.004), a higher rate of nosocomial infections (OR, 1.9; 95% CI, 1.2–3.0; $P = 0.004$), and more cardiac or respiratory dysfunction (OR, 2.1; 95% CI, 1.5–3.0; $P < 0.001$). The transfused group had a longer PICU length of stay (7.5 d in nontransfused vs. 9.3 d in transfused, $P = 0.0002$) and, for children ventilated beyond 48 hours (n = 421 [204 nontransfused and 217 transfused]), a longer length of mechanical ventilation (7.5 d in nontransfused vs. 9.6 d in transfused, $P = 0.003$). Of note, 12 of 15 deaths (80%) in the transfused group occurred in patients who had received more than four transfusions in the PICU.

The number of patients who received a transfusion after 48 hours was 162 (17%). Predictors for receiving an RBC transfusion after the first 2 days in the PICU were calculated using a multivariate logistic regression analysis, excluding only those children receiving ECMO on PICU Days 1–2 (n = 19). Factors predictive of a later transfusion in the bivariate analysis were tested in the multivariate model and are reported in Table 3. Significant predictors of receiving a transfusion more than 48 hours after PICU admission were age of 28 days or younger, RBC transfusion

on PICU Days 1 or 2, presence of severe or moderate anemia, presence of shock on PICU admission, admission because of trauma, admission category of cardiovascular or "other," baseline PRISM III score of more than 5, having a hematologic/oncologic comorbid condition, and high mean daily volume/kg of blood loss from blood draws. Factors not predictive in the univariate analysis were sex, race, and admission type (medical, surgical nontrauma, trauma).

The reason for transfusion in the PICU was reported by the prescribing physician and is presented in Table 4. Low Hb was the most common reason listed (42%), and this category had a significantly lower mean pretransfusion Hb than the other groups ($P < 0.001$). Bone marrow suppression and specific technologies were infrequent primary reasons for transfusion, but those patients had many more transfusion events per patient. Mean number of PICU transfusions varied significantly between reason groups ($P < 0.0001$).

There was marked variability in Hb values before transfusion. Table 5 shows the mean and median pretransfusion Hb plus intraquartile ranges for the first transfusion by age, admitting type (medical vs. surgical/trauma), and severity of illness (PRISM III score). Younger children had a higher mean pretransfusion Hgb ($P < 0.0001$). Children with a lower PRISM III score (≤5) and a medical admission type had lower pretransfusion Hb levels ($P < 0.001$).

TABLE 3. PREDICTORS OF TRANSFUSION AFTER PEDIATRIC INTENSIVE CARE UNIT DAY 2 (n = 958)*

Effect	Odds Ratio (95% Wald confidence limits)	*P* Value
Age category		
<28 d	2.4 (1.2–5.1)	
≥28 d to <2 yr	1.3 (0.8–2.0)	
≥2 yr to <5 yr	0.8 (0.5–1.5)	
≥5 yr to <12 yr	Reference	
≥12 yr to ≤18 yr	0.8 (0.5–1.3)	0.03
Female vs. male	1.3 (0.9–1.7)	0.13
Race		
White	Reference	
Asian	2.1 (0.7–6.2)	
Black	0.7 (0.4–1.2)	
Other	0.6 (0.4–1.0)	0.09
No transfusion ICU Days 1–2	0.5 (0.4–0.8)	<0.001
Anemia severity		
Severe (Hb < 7g/dl)	7.5 (3.5–15.7)	
Moderate (Hb > 7 and <10 g/dl)	2.0 (1.4–2.8)	
Mild (Hb > 10 g/dl)	Reference	<0.001
Primary admitting type		
Medical	0.7 (0.3–1.3)	
Surgical, nontrauma	0.3 (0.2–0.5)	
Trauma	Reference	<0.0001
Primary admission category		
Cardiovascular	2.1 (1.3–3.4)	
Respiratory	Reference	
Central nervous system	0.8 (0.5–1.4)	
Other†	1.9 (1.2–3.1)	<0.001
PRISM III score		
0	0.7 (0.5–1.1)	
1–5	0.6 (0.5–0.9)	
>5	Reference	0.03
Chronic conditions		
Hematology/oncology comorbidity	1.8 (1.1–3.1)	0.02
Blood loss via blood draws		
Above mean daily volume/kg loss	1.1 (1.0–1.2)	0.01

Definition of abbreviations: Hb = hemoglobin; ICU = intensive care unit; PRISM = Pediatric Risk of Mortality.

* Children on extracorporeal membranous oxygenation Days 1–2 were excluded (n = 19).

† Other included gastrointestinal, hematology, endocrine, or renal.

TABLE 4. REASON FOR FIRST TRANSFUSION BY ORDERING PHYSICIAN (n = 476)

	No. (%)	Mean No. of PICU Transfusion Events/Child (SD) [median]	Mean Pretransfusion Hemoglobin, g/dl (SD) [median]
Low hemoglobin	198 (42)	3.1 (3.5) [2.0]	8.2 (2.4) [7.9]
Unknown	80 (17)	1.8 (2.1) [1.0]	10.4 (3.0) [9.9]
Acute blood loss (gastrointestinal bleeding/surgical procedures*)	78 (16)	4.8 (6.2) [2.0]	10.5 (2.5) [10.6]
Cardiovascular insufficiency†	41 (9)	3.6 (3.3) [2.0]	10.4 (2.3) [10.0]
Specific technologies‡	35 (7)	10.9 (8.2) [10.0]	10.7 (3.1) [10.3]
Respiratory insufficiency§	34 (7)	2.9 (1.9) [2.0]	9.6 (2.2) [9.5]
Bone marrow suppression/coagulopathy	9 (2)	5.2 (5.4) [3.0]	8.8 (1.4) [9.4]

Definition of abbreviation: PICU = pediatric intensive care unit.

Data from ordering physician first-ranked indication. Mean number of PICU transfusions varied significantly between transfusion reason groups ($P < 0.0001$). Mean pretransfusion hemoglobin significantly lower in the low hemoglobin group ($P < 0.001$).

* Surgical procedures: elective or emergent surgery, trauma.

† Cardiovascular: cardiac dysfunction, hypotension, cyanotic heart disease.

‡ Specific technologies: extracorporeal membranous oxygenation, hemodialysis, plasmaphoresis, hemofiltration, exchange transfusion.

§ Respiratory: enhanced oxygen delivery, low Pa_{O_2}, respiratory insufficiency.

Median daily Hb values were lower for children who received a transfusion compared with those who did not ($P < 0.0001$; Figure 4). Excluding neonates, Hb values for 75% of children for the first 14 days of ICU stay were 8.4 g/dl or greater in those who did not receive a transfusion and 8.1 g/dl or more in those who received one or more PRBC transfusion.

DISCUSSION

This is the first large, multicenter, prospective study of anemia, blood loss, and transfusion practices in critically ill children. Anemia was a common problem, affecting 74% of these children during or immediately before PICU admission. Blood loss via blood draws was particularly significant in the younger age groups. Almost half of the study population received at least one RBC transfusion. The majority (74%) received their first transfusion in the first 2 days after admission and only 4% received it after the first week. These data provide evidence

TABLE 5. PRETRANSFUSION HEMOGLOBIN VALUES

	No. (%)	Mean g/dl (SD) [Δ from anemia cutoff]*	Median g/dl (IQR)	*P* Value
Overall	451	9.7 (2.7)	9.2 (7.7–11.4)	
Age				
<28 d	56 (12)	12.3 (2.3) [−2.2]	12.5 (10.4–14.2)	
≥28 d to <2 yr	193 (43)	9.8 (2.6) [−1.1]	9.2 (7.8–11.6)	
≥2 yr to <5 yr	55 (12)	9.7 (2.8) [−1.6]	9.0 (7.5–11.3)	
≥5 yr to 12 yr	66 (15)	8.8 (1.9) [−1.6]	8.3 (7.6–10.0)	
≥12 yr to <18 yr	81 (18)	8.7 (2.4) [−3.9]	8.2 (7.0–9.8)	<0.001
Admission type				
Medical	195 (43)	8.7 (2.0)	8.2 (7.2–10.0)	
Nonmedical†	256 (57)	10.6 (2.8)	10.3 (8.4–12.7)	<0.001
Severity of illness				
PRISM III ≤5	253 (56)	9.2 (2.4)	8.8 (7.5–10.5)	
PRISM III >5	198 (44)	10.4 (2.8)	10.0 (8–12.7)	<0.001

Definition of abbreviations: IQR = 25–75% intraquartile range; PRISM = Pediatric Risk of Mortality.

* ΔChange from anemia cutoff: difference of mean pretransfusion hemoglobin from cutoff for definition of anemia for that age group.

† Nonmedical: elective or emergent surgical admission or trauma.

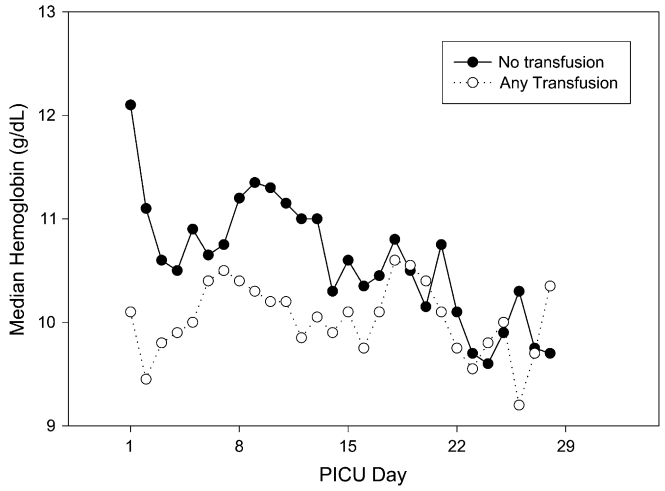

Figure 4. Median hemoglobin by day and transfusion group (age > 2 and < 18 yr). Mean daily hemoglobin for the first 14 days was significantly less in patients who received a transfusion ($P < 0.001$).

against prophylactic therapy with erythropoietin to prevent blood transfusions in the PICU setting, and focus more emphasis on blood loss prevention. After correction for age and illness severity, the increased length of stay and complications shown in the children who received a transfusion provide supportive evidence that efforts at minimizing transfusions should continue.

Most data available on incidence of anemia and transfusion practices in the children come from neonates, which do not provide clear guidance for the highly variable PICU population (18–20). Anemia in critically ill children is almost always treated by blood transfusion, and transfusions have been associated with increased PICU utilization (21). Published reports suggest considerable variability in practice. A single-center Canadian study revealed that 15% of all children in the ICU received at least one transfusion (22), whereas a British single-center study reported that 48% of all children in the PICU received at least one transfusion (23). Surveys of physician opinion suggest wide variability of Hb values used to justify RBC transfusion decisions in children (24–26). Our multicenter international study showed that the proportion of children who received at least one RBC transfusion while they were in the PICU was 49%.

The rate of anemia observed in our study population was higher than expected. These data mimic the results reported on adults by Vincent and colleagues in their prospective blood loss and transfusion survey in European ICUs, with similar rates of anemia on admission (33 vs. 36%) (11). However, the prevalence of anemia in the PICU is greater due to the additional 41% who developed anemia in the PICU.

The impact of anemia on the outcome of critically ill children is not well understood. Some data suggest that severe anemia may be detrimental to critically ill children with septic shock or hemodynamic compromise (27–30). Anemia was associated with a worse outcome in the Corwin study, a descriptive prospective study that included 4,892 consecutive critically ill adults from 213 American ICUs (31). The same association was observed in 3,534 adults from 146 Europeans ICUs (11). The postoperative risk of death increases significantly when Hb concentration drops below 4 g/dl (32). Three prospective studies run in Kenya involving, respectively, 2,433, 1,223, and 1,269 hospitalized children showed that the risk of death was significantly higher if their Hb concentration was lower than 5 g/dl and if they did not receive an RBC transfusion; these children were not critically ill, but most had respiratory symptoms (33–35). Therefore, severe anemia seems to be an independent risk factor for death in sick patients, at least when the Hb concentration drops below 5 g/dl. On the other hand, a large multicenter randomized clinical trial, the TRIPICU (Transfusion Requirements in the Pediatric Intensive Care Unit) study, showed that a restrictive RBC transfusion strategy in which the threshold Hb concentration to prescribe a transfusion was 7 g/dl was not inferior to a liberal strategy with a threshold of 9.5 g/dl in stable, critically ill children (36). This suggests that an RBC transfusion is probably not useful in stable children if their Hb concentration is above 7 g/dl. The Hb concentration that should prompt pediatric intensivists to prescribe an RBC transfusion in unstable children remains to be determined. Higher Hb concentrations may be required in children with greater severity of illness (e.g., shock) and in specific subpopulations (e.g., postoperative cardiac surgery).

Small body size and small total blood volume make children vulnerable to anemia secondary to blood draws despite the use of microsampling techniques. Our findings point out the need for future studies of blood conservation strategies via phlebotomy in the PICU. The median blood volume loss was 5.0 ml/day in our study, which is markedly less than the 41 ml/day reported by Vincent and colleagues in adult ICUs (11). However, the degree of blood volume loss remains significant, particularly because almost half of our population was younger than 24 months. The total blood volume of a 5-kg child is about 400 ml in comparison to 5 L in a typical adult. Younger children have higher circulating blood volumes per kilogram (80 ml/kg) than older children and adults (70 ml/kg) (37), but the burden on them from iatrogenic blood loss remains significantly higher due to their overall lower blood volumes. Blood loss was not predictive of later anemia, most likely because such a high percentage of patients were anemic (74%) and our model did not determine whether blood draws led to more severe anemia. More importantly, we noted that blood loss secondary to blood draws early in admission was predictive of later transfusion.

Vincent and coworkers reported a transfusion rate of 34% in their adult trial. Our findings of a 49% transfusion rate are higher, potentially due to a different transfusion threshold practiced in the PICU. The mean pretransfusion Hb in the adult trial was 8.4 ± 1.3 g/dl compared with our findings of 9.7 ± 2.7 g/dl (11). The results of the TRIPICU study suggest that it is safe not to give RBC transfusion to stable, critically ill children if their Hb concentration is higher than 7 g/dl (35). In our study, the children who could be considered more stable (based on low PRISM III scores < 5) and who received a transfusion (n = 253) had a mean pretransfusion Hb of 9.23 ± 2.4 g/dl. Markedly fewer children in these groups might receive a transfusion if the results of the TRIPICU study are applied.

Almost three-quarters of our patients received their transfusions in the first 2 days. Unless the criteria for RBC transfusion changes, it is unlikely that therapies such as erythropoietin will be of benefit to prevent transfusions given the time required for this therapy to affect a change in Hb in critically ill patients (38). The use of erythropoietin in the PICU may merit further study, however, because of recent evidence demonstrating a mortality benefit in critically ill adults, which was independent of its effect on Hb (39).

This study represents the largest assessment of the RBC transfusion rationale among physicians caring for critically ill patients. Low Hb was almost twice as common as blood loss as the primary reason for transfusion. Therefore, clearer guidelines for Hb values that should trigger a transfusion would benefit clinicians. On the other hand, our data suggest that some attention must also be paid to other justifications, such as the severity of illness and blood loss.

The strengths of our study include the size of the study population, and the focus on the relationship between PICU day and transfusion risk. We noted that those children staying in the PICU more than 48 hours are at higher risk for transfusion. The proportion of children who received an RBC transfusion was 17% in 216 children who stayed in the PICU less than 2 days in comparison to 49% in the 977 who stayed more than 48 hours (*see* Table E2). The generalizability to the entire PICU population must account for the fact that only approximately 20% of PICU patients have a length of stay greater than 48 hours.

In this long-stay population, our data show that, when corrected for severity of illness, transfusions were associated with significantly worse outcomes. This has not been shown previously in any prospective study in the PICU and warrants a serious look into the use of transfusions in this population. Our data are consistent with the adult literature by Vincent and colleagues and Corwin and coworkers, which also showed longer length of stay and increased morbidity and mortality in the transfused ICU patients (11, 31). However, this was contrasted by the more recent analysis of adult ICU patients, which showed no mortality increase in patients who received a transfusion (40). This discrepancy has been suggested to be due to PRBC factors such as leukoreduction and older age of blood. The storage age of blood of greater than 2 weeks was reported to be an independent risk factor of mortality in adult cardiac surgical patients (41). Our findings of worse outcomes in the PICU children who received a transfusion, however, were with blood that had an 86% leukoreduction rate and 65% with storage age less than 14 days. Therefore, the effect of transfusion in our population appears to be independent of the suspected PRBC factors. A single-center retrospective study of transfusions in critically ill children by Kneyber and colleagues also found increased mortality and morbidity in children who received a transfusion, and all of their transfusions were with leukoreduced blood (42). The finding that a majority of the deaths in this study occurred in patients with more than four transfusions raises the need to better understand the effects of transfusion in unstable children. There was no increased death rate in the children who received a single or double transfusions. We did confirm the findings of Slonim and coworkers that complications directly related to the administration of PRBCs in children are rare (43).

In conclusion, the burden of anemia, blood loss, and transfusions in the PICU population are significant. Efforts to develop guidelines are clearly needed. Prospective studies taking into account the data provided in this large multicenter epidemiologic study should be undertaken to estimate the clinical impact of measures aiming to decrease blood draws, to prevent or treat anemia, and to decrease transfusions for critically ill children.

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***Participating PALISI investigators in the United States and Canada are as follows*:** Shamile Abd-Allah, M.D., Loma Linda University Children's Hospital, Loma Linda, CA; Roger Barton, M.D., Children's Hospital of Saint Francis, Tulsa, OK; Scot Bateman, M.D., Adrienne Randolph, M.D., Heather Healey, R.N., Children's Hospital, Boston, MA; James Besunder, M.D., Akron Children's Hospital, Akron, OH; Jeffrey Blumer, M.D., Rainbow Babies and Tod Hospital, Cleveland, OH; Ira Cheiftez, M.D., Andora Bass, M.D., Duke Medical Center, Durham, NC; Heidi Dalton, M.D., Children's National Medical Center, Washington, DC; Emily Dobyns, M.D., Children's Hospital, Denver, CO; Jill Fitch, M.D., Children's Hospital, Columbus, OH; Rainer Gedeit, M.D., Children's Hospital Wisconsin, Milwaukee, WI; Brahm Goldstein, M.D., Doernbecher Children's Hospital, Oregon Health and Science University, Portland, OR; Marek Grzeszczak, M.D., Vanderbilt Children's Hospital, Nashville, TN; James H. Hanson, M.D., Children's Hospital and Research Center Oakland, Oakland, CA; Rashed Hasan, M.D., Hurley Medical Center, Flint, MI; Brian Jacobs, M.D., Cincinnati Children's Hospital, Cinncinati, OH; Larry Jefferson, M.D., Baylor College of Medicine, Houston, TX; Daniel Levin, M.D., Dean Jarvis, R.N., Children's Hospital at Dartmouth, Hanover, NH; Barry Markovitz, M.D., Washington University, St. Louis, MO; Christopher Newth, M.D., Lori Auw, R.C.T., Children's Hospital of Los Angeles, Los Angeles, CA; Vipul Patel, M.D., Dayton Children's Hospital, Dayton, OH; Steven Pon, M.D., Charlene S. Correa, B.A., New York Presbyterian Hospital, New York, NY; Edward Seferian, M.D., Mayo Clinic, Rochester, MN; Neal J. Thomas, M.D., Joseph Hess, R.N., Jennifer Stokes, R.N., Penn State Children's Hospital, Hershey, PA; Douglas Willson, M.D., University of Virginia, Charlottesville, VA; Peter Cox, M.D., Hospital for Sick Children, Toronto, Canada; Ari Joffe, M.D., University of Alberta, Edmonton, Canada; Jacques Lacroix, M.D., Hospital Sainte-Justine, Montreal, Canada; Kusum Menon, M.D., Children's Hospital of Eastern Ontario, Ottowa, Canada; David Wensley, M.D., Children's and Women's Hospital, Vancouver, Canada.

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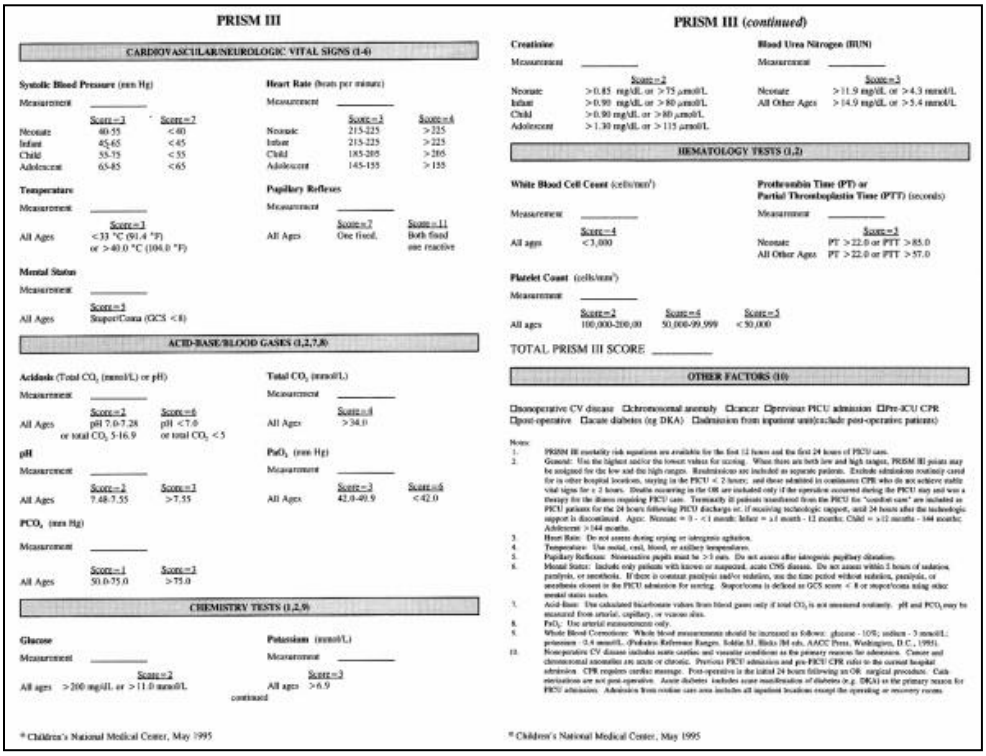
Appendix 3.

PRISM III and PELOD scores of severity

PRISM III: An updated Pediatric Risk of Mortality score.
Pollack, Murray; Patel, Kantilal; Ruttimann, Urs
Critical Care Medicine. 24(5):743-752, May 1996.



PRISM III

CARDIOVASCULAR/NEUROLOGIC VITAL SIGNS (1-4)

Systolic Blood Pressure (mm Hg)
Measurement _____

	Score = 3	Score = 7
Neonate	40-55	< 40
Infant	45-65	< 45
Child	55-75	< 55
Adolescent	65-85	< 65

Heart Rate (beats per minute)
Measurement _____

	Score = 2	Score = 6
Neonate	215-225	> 225
Infant	215-225	> 225
Child	185-205	> 205
Adolescent	145-155	> 155

Temperature
Measurement _____

	Score = 3	Score = 7
All Ages	< 33 °C (91.4 °F) or > 40.0 °C (104.0 °F)	

Pupillary Reflexes
Measurement _____

	Score = 7	Score = 11
All Ages	One fixed,	Both fixed one reactive

Mental Status
Measurement _____

	Score = 5
All Ages	Stupor/Coma (GCS < 8)

ACID-BASE/BLOOD GASES (1,2,7,8)

Acidosis (Total CO_2 (mmol/L) or pH)
Measurement _____

	Score = 2	Score = 6
All Ages	pH 7.0-7.28 or total CO_2 5-16.9	pH < 7.0 or total CO_2 < 5

Total CO_2 (mmol/L)
Measurement _____

	Score = 4
All Ages	> 34.0

pH
Measurement _____

	Score = 2	Score = 3
All Ages	7.48-7.55	> 7.55

PaO_2 (mm Hg)
Measurement _____

	Score = 3	Score = 6
All Ages	42.0-49.9	< 42.0

PCO_2 (mm Hg)
Measurement _____

	Score = 1	Score = 3
All Ages	50.0-75.0	> 75.0

CHEMISTRY TESTS (1,2,9)

Glucose
Measurement _____

	Score = 2
All ages	> 200 mg/dL or > 11.0 mmol/L

Potassium (mmol/L)
Measurement _____

	Score = 3
All ages	> 6.9

continued

* Children's National Medical Center, May 1995

PRISM III *(continued)*

Creatinine
Measurement _____

	Score = 2
Neonate	> 0.85 mg/dL or > 75 μmol/L
Infant	> 0.90 mg/dL or > 80 μmol/L
Child	> 0.80 mg/dL or > 80 μmol/L
Adolescent	> 1.30 mg/dL or > 115 μmol/L

Blood Urea Nitrogen (BUN)
Measurement _____

	Score = 3
Neonate	> 11.9 mg/dL or > 4.3 mmol/L
All Other Ages	> 14.9 mg/dL or > 5.4 mmol/L

HEMATOLOGY TESTS (1,2)

White Blood Cell Count (cells/mm³)
Measurement _____

	Score = 4
All ages	< 3,000

Prothrombin Time (PT) or Partial Thromboplastin Time (PTT) (seconds)
Measurement _____

	Score = 3
Neonate	PT > 22.0 or PTT > 85.0
All Other Ages	PT > 22.0 or PTT > 57.0

Platelet Count (cells/mm³)
Measurement _____

	Score = 2	Score = 4	Score = 5
All ages	100,000-200,00	50,000-99,999	< 50,000

TOTAL PRISM III SCORE _____

OTHER FACTORS (10)

☐noncardiac CV disease ☐chromosomal anomaly ☐cancer ☐previous PICU admission ☐Pre-ICU CPR ☐post-operative ☐acute diabetes (eg DKA) ☐admission from inpatient unit(exclude post-operative patients)

Notes:
1. PRISM III mortality risk equations are available for the first 12 hours and the first 24 hours of PICU care.
2. General: Use the highest and/or the lowest values for scoring. When there are both low and high ranges, PRISM III points may be assigned for the low and the high ranges. Readmissions are included as separate patients. Exclude admissions routinely cared for in other hospital locations, staying in the PICU < 2 hours, and those admitted in continuous CPR who do not achieve stable vital signs for ≥ 2 hours. Deaths occurring in the OR are included only if the operation occurred during the PICU stay and was a therapy for the illness requiring PICU care. Terminally ill patients transferred from the PICU for "comfort care" are included as PICU patients for the 24 hours following PICU discharge or, if receiving technologic support, until 24 hours after the technologic support is discontinued. Ages: Neonate = 0 - < 1 month; Infant = ≥1 month - 12 months; Child = ≥12 months - 144 months; Adolescent ≥144 months.
3. Heart Rate: Do not assess during crying or iatrogenic agitation.
4. Temperature: Use rectal, cecil, blood, or axillary temperatures.
5. Pupillary Reflexes: Nonreactive pupils must be >3 mm. Do not assess after iatrogenic pupillary dilatation.
6. Mental Status: Include only patients with known or suspected, acute CNS disease. Do not assess within 2 hours of sedation, paralysis, or anesthesia. If there is constant paralysis and/or sedation, use the time period without sedation, paralysis, or anesthesia closest to the PICU admission for scoring. Stupor/coma is defined as GCS score < 8 or stupor/coma using other mental status scales.
7. Acid-Base: Use calculated bicarbonate values from blood gases only if total CO_2 is not measured routinely. pH and PCO_2 may be measured from arterial, capillary, or venous sites.
8. PaO_2: Use arterial measurements only.
9. Whole Blood Correction: Whole blood measurements should be increased as follows: glucose - 10%; sodium - 3 mmol/L; potassium - 0.4 mmol/L. (Pediatric Reference Ranges. Soldin SJ, Hicks JM eds. AACC Press, Washington, D.C., 1995).
10. Noncardiac CV disease includes acute cardiac and vascular conditions as the primary reasons for admission. Cancer and chromosomal anomalies are acute or chronic. Previous PICU admission and pre-PICU CPR refer to the current hospital admission. CPR requires cardiac massage. Post-operative is the initial 24 hours following an OR surgical procedure. Code elevations are not post-operative. Acute diabetes includes acute manifestation of diabetes (e.g. DKA) as the primary reason for PICU admission. Admission from routine care area includes all inpatient locations except the operating or recovery rooms.

* Children's National Medical Center, May 1995

PELOD

Multiple Organ Dysfunction Score: A reliable descriptor of a complex clinical outcome.
Marshall, John; Cook, Deborah; MD MSc, FRCPC; Christou, Nicolas; MD PhD, FCCM; Bernard, Gordon; Sprung, Charles; MD JD, FCCM; Sibbald, William
Critical Care Medicine. 23(10):1638-1652, October 1995.

Organ System	Score				
	0	1	2	3	4
Respiratory[a] (Po_2/Fio_2 ratio)	>300	226–300	151–225	76–150	≤75
Renal[b] (serum creatinine)	≤100	101–200	201–350	351–500	>500
Hepatic[c] (serum bilirubin)	≤20	21–60	61–120	121–240	>240
Cardio-vascular[d] (PAR)	≤10.0	10.1–15.0	15.1–20.0	20.1–30.0	>30.0
Hematologic[e] (platelet count)	>120	81–120	51–80	21–50	≤20
Neurologic[f] (Glasgow Coma Score)	15	13–14	10–12	7–9	≤6

[a]The Po_2/Fio_2 ratio is calculated without reference to the use or mode of mechanical ventilation, and without reference to the use or level of positive end-expiratory pressure; [b]the serum creatinine concentration is measured in μmol/L, without reference to the use of dialysis; [c]the serum bilirubin concentration is measured in μmol/L; [d]the pressure-adjusted heart rate (PAR) is calculated as the product of the heart rate (HR) multiplied by the ratio of the right atrial (central venous) pressure (RAP) to the mean arterial pressure (MAP): PAR = HR × RAP/mean BP; [e]the platelet count is measured in platelets/mL 10^{-3}; [f]the Glasgow Coma Score is preferably calculated by the patient's nurse, and is scored conservatively (for the patient receiving sedation or muscle relaxants, normal function is assumed, unless there is evidence of intrinsically altered mentation).

Appendix 4.

Université de Montréal

HyperOsmolar Therapy for Pediatric Traumatic Brain Injury « The HOT PEABRAIN Trial »

Protocole de Recherche

Par

Geneviève Morisette

Nadia Roumeliotis

UNIVERSITÉ DE MONTRÉAL

Protocole de Recherche

HyperOsmolar Therapy for Pediatric Traumatic Brain Injury « The HOT PEABRAIN Trial »

Par
Geneviève Morissette
Nadia Roumeliotis

Maitrise en sciences biomédicales
Département de médecine sociale et préventive

Travail présenté à Benoit Masse
Dans le cadre du cours MSO-6075
Étude et devis expérimentaux

Mai 2015

1. LA NÉCESSITÉ DE RÉALISER UN ESSAI

1.1 Le problème sur lequel portera l'essai

Les accidents sont la première cause de décès chez les enfants âgés de 1 à 16ans[1], et la première cause de décès parmi eux est le traumatisme crânien sévère. La sévérité du traumatisme crânien est typiquement évaluée par un score clinique, le Score de Glascow, qui évalue la réponse motrice, verbale et oculaire du patient[2]. Le traumatisme crânien (TCC) sévère se définit par un Score de Glasgow <8 et nécessite une prise en charge agressive vu la haute mortalité qui y est associée. La prise en charge du traumatisme crânien nécessite une évaluation radiologique, une consultation neurologique et un contrôle étroit de l'œdème cérébral qui se développe sur les 48-72h après l'évènement. Une hypertension intracrânienne (HTIC) se caractérise par une pression intracérébrale (PIC) > 20mmHg, mesurée avec un moniteur de pression intracrânienne placé dans le tissu cérébral après l'évènement. Une HTIC prolongée est associée à un mauvais pronostic sur le plan neurologique et à une mortalité augmentée[3].

Des lignes directrices existent pour la prise en charge du traumatisme cranio-cérébral sévère chez l'adulte et chez l'enfant[4,5,6]. Cette prise en charge inclut le monitoring invasif de la pression intracrânienne et l'utilisation d'agents hyperosmolaires : le mannitol et le salin hypertonique 3% pour traiter une pression intracrânienne élevée.

Les principales théories quand au mécanisme d'action du salin et du mannitol sont la réduction de la viscosité sanguine de même qu'une réduction de l'eau intracellulaire intracérébrale due à un mouvement oncotique d'eau vers le compartiment intravasculaire.

Les études adultes démontrent un bénéfice sur l'HTIC pour l'utilisation du salin hypertonique (7%) par rapport au mannitol[7,8], par contre aucune étude ne démontre des bénéfices cliniques soutenu à long terme pour l'un ou l'autre[9]. Aucune donnée pédiatrique n'existe quand à la supériorité d'un agent par rapport à l'autre, tant sur la diminution de la pression intracrânienne que sur les effets cliniques à long terme. Actuellement, l'utilisation du mannitol ou du salin hypertonique pour une PIC élevée chez l'enfant se fait de façon relativement aléatoire selon la préférence du médecin traitant ou du centre traitant. Bennett et al. ont étudié l'utilisation de ces agents dans une étude de base de données rétrospectives, et ont démontré une grande variabilité de l'utilisation du salin et du mannitol selon l'âge et le centre de traitement[10]. Nous souhaitons déterminer si un agent hyperosmolaire est supérieur à l'autre pour diminuer la pression intracrânienne en phase aigue.

1.2 Principales questions auxquelles la recherche tentera de répondre

Dans la prise en charge du traumatisme crânien sévère chez l'enfant, y-a-t'il une différence significative entre le salin hypertonique (3%) et le mannitol (20%) sur la réduction de la pression intracrânienne dans les deux heures après le traitement? Cette différence persiste-elle dans les 4 heures suivantes?

De plus, quels sont les taux de complications majeures de ces agents hyperosmolaires? Lequel est associé à des co-interventions plus importantes? Les complications potentielles et problèmes secondaires à chercher dans notre étude seront l'hypotension, l'hypernatrémie et l'insuffisance rénale aigue (IRA).

1.3 Pourquoi l'essai doit-il être réalisé à ce moment-ci?

Actuellement, il existe une équipoise clinique quand à l'utilisation des agents hyperosmolaires pour la prise en charge de la PIC. Les pratiques hospitalières se basent surtout sur le confort du médecin traitant et non sur une science déterminée. Plusieurs études adultes ont comparé le salin hypertonique et le mannitol pour la pression intracrânienne. Vialet et al, ont comparé deux charges iso volumiques de salin et mannitol (4.8 mOsm/kg vs 2.3 mOsm/kg) et ont démontré une supériorité du salin pour la réduction de l'hypertension intracrânienne[11]. Harutjunyan et al. ont démontré une supériorité du salin 7,2%/starch par rapport au mannitol 15% pour réduire la pression intracrânienne chez les patients adultes de neurochirurgies[8]. Battison et al. ont comparé une solution équimolaire de salin/dextran (110cc) par rapport au mannitol (230cc), et ont démontré une diminution plus importante et plus soutenue avec la solution salin/dextran[12]. Francony et al. ont ensuite comparé des doses équimolaires de mannitol et salin hypertonique (sans dextran) et n'ont pas trouvé de différence entre les traitements sur la diminution de la pression intracrânienne à 60 et 120 minutes[7]. Il y a donc beaucoup de variabilité quant aux protocoles et aux solutions de traitement des ces différentes études. Malgré une tendance pour des meilleurs résultats avec le salin, aucune étude n'a démontré un effet clinique bénéfique à long terme. En pédiatrie, aucune étude comparant ces deux agents n'a été effectuée pour déterminer leur efficacité sur la diminution de la pression intracrânienne, et les deux traitements sont considérés comme standard pour la prise en charge de l'HTIC. De plus, les dernières recommandations internationales mentionnaient l'absence de données pour comparer les deux agents chez l'enfant et encourageaient les recherches dans ce domaine.

1.4 Études systématiques pertinentes et analyse de la nécessité de réaliser l'essai proposé

Mortazavi et al. ont effectué une méta-analyse sur le salin hypertonique dans la réduction de l'HTIC chez l'adulte[13]. Parmi les études publiées, 12 études ont comparé le salin hypertonique et le mannitol, et 6 étaient des études randomisées contrôlées (ECR). Les études étaient relativement petites (*n* max =34) et variables quand aux paramètres étudiés et aux bolus osmolaires reçus, mais dans l'ensemble neuf d'entre elles ont suggéré une supériorité du salin hypertonique et trois n'ont montré aucune différence. Kamel et al. ont aussi effectué une méta-analyse incluant 5 ECR comparant les deux traitements et ont conclu à une supériorité du salin hypertonique pour une diminution de la pression intracrânienne[14]. Aucune des ces études n'a été effectuée sur une population pédiatrique, et il n'y a aucun RCT dans ce domaine en pédiatrie.

1.5 Quelle utilisation sera faite des résultats de l'essai ?

Cette étude est en fait une étude primaire afin 1) d'établir si le mannitol et le salin hypertonique sont utiles pour la réduction de la PIC de façon significative en pédiatrie 2) d'établir quel agent réduit de façon plus significative (supériorité) la pression intracrânienne 3) de préparer des études futures en pédiatrie sur la réduction à plus long terme de la PIC avec les agents hyperosmolaires 4) évaluer l'impact clinique (mortalité) et le devenir neurologique de ces patients 5) tenter de faire des recommandations pédiatriques sur l'utilisation de ces agents hyperosmolaires.

1.6 Les risques liés à la sécurité de ceux qui participent à l'essai

Les risques reliés à la sécurité de ceux qui participent à l'essai sont très faibles. En effet, ils reçoivent le même traitement standard que tous les autres patients ayant la même pathologie et qui ne sont pas dans l'étude. Cependant, il est fréquent que ces patients reçoivent à la fois du salin hypertonique et du mannitol au cours d'une même hospitalisation, si la réponse ne satisfait pas le clinicien ou s'il y a un changement de médecin traitant. C'est pour cette raison que nous avons décidé de limiter l'étude à une période de quatre heures seulement, afin de ne pas limiter les patients à un seul des deux agents hyperosmolaires pour une période prolongée, ne sachant pas s'il y avait un bénéfice à alterner ou à additionner les agents ensemble.

2. L'ESSAI PROPOSE

2.1 La méthode d'expérimentation proposée

Le devis de l'étude proposé en est un de supériorité. C sera une étude multicentrique, randomisée contrôlée à double insu comparant des doses équimolaires de salin hypertonique 3% au mannitol 20% dans la réduction de la PIC chez l'enfant avec TCC sévère.

Notre critère d'évaluation primaire sera le changement de la PIC (Δ) dans les deux heures après chaque traitement; soit salin hypertonique ou mannitol. Nos critères d'évalation secondaires seront les effets adverses de ces traitements, soient; hypotension, hypernatrémie, IRA, une osmolarité sanguine élevée, de même que les co-interventions nécessaires pour diminuer l'HTIC et le changement de pression intracrânienne soutenu après 4h.

2.2 Description des interventions prévues en cours d'essai

Nous avons choisi de comparer deux traitements couramment utilisés dans la prise en charge de l'HTIC de l'enfant. Les patients seront randomisés dans deux bras : mannitol 20% ou salin hypertonique 3%. Il n'y a pas de groupe contrôle avec placebo puisque les deux agents sont considérés comme un standard de traitement dans la prise en charge de l'HTIC chez l'enfant avec TCC sévère.

<u>Dépistage et Inclusion</u>

Le dépistage des patients aura lieu lors de leur arrivée au centre tertiaire avec TCC sévère. Après l'évaluation par les soins intensifs et la neurochirurgie, le patient sera considéré pour l´étude s'il y a installation de monitoring de la PIC en salle d'opération. Si les critères d'inclusions sont présents, le personnel de recherche sera appelé et fera le consentement de l'étude avec les parents, après le consentement de la pose de moniteur de PIC. Si les parents ne sont pas présents, ils pourront être rejoints par téléphone afin d'obtenir un pré-consentement qu'ils pourront signer à leur arrivée à l'hôpital.

<u>Prise en Charge</u>

À l'admission aux soins intensifs, après l'installation du moniteur de PIC, la prise en charge se fera de façon standard suivant l'algorithme décisionnel aidant à la prise en charge de TCC. Cet algorithme sera inclus dans le dossier du patient et guidera l'équipe traitante quand aux thérapies envisagées. L'objectif d'inclure cet algorithme dans le

protocole de recherche vise la standardisation de la thérapie pour la prise en charge de ces patients (Voir Annexe 1). Tout patient sera intubé et ventilé, avec sédation et analgésie en perfusion continue. La température sera contrôlée pour éviter l'hyperthermie, et des agents vasoactifs seront utilisés pour maintenir une pression moyenne adéquate.

Monitoring et Surveillance

Les signes vitaux (pris en continu) seront enregistrés aux 15 minutes pendant les 2h après le traitement, incluant fréquence cardiaque, la tension artérielle (TA), la fréquence respiratoire et la température. Le score de Glascow sera évalué et noté aux heures. La PIC et la pression de perfusion cérébrale (PPC) seront aussi notées aux 15 minutes dans les 2h suivant le traitement, et aux 30 minutes jusqu'à 4h post traitement. La diurèse sera notée toutes les heures. Les prélèvements de gaz artériel et électrolytes seront pris 4h post traitement.

Intervention

Chaque patient avec une PIC élevée (>20mmHG) soutenue pendant plus de cinq minutes, ou chez qui le médecin traitant juge qu'un agent hyperosmolaire est indiqué, recevra mannitol ou salin hypertonique selon son allocation. L'allocation sera faite par le pharmacien selon la liste de randomisation qui lui aura été confiée.

Les doses d'agents hyperosmolaires seront équimolaires, donc la même charge d'osmoles sera livrée à chaque patient, soit 3 Osm/kg. Le volume de salin 3% ayant une osmolarité un peu plus petite (1027 Osm/L vs 1100 Osm/L pour le mannitol) le volume sera complété avec une très petite quantité d'eau stérile pour que les deux solutions aient le même volume et osmolarité. Chaque agent sera préparé de façon confidentielle par la pharmacie et livré en seringue opaque avec tubulure opaque, identifié «agent hyperosmolaire».

Le médecin et le personnel soignant seront aveugles quand à l'agent en cours. Tout autre traitement jugé nécessaire devrait être identique dans les deux groupes. Si le médecin traitant initie une thérapie pour la prise en charge de l'HTIC durant les 2h post traitement, ceux-ci seront considérés comme des co-interventions (coma barbiturique, hypothermie, hyperventilation). La diminution de la pression intracrânienne moyenne, calculée par une moyenne des PIC prises aux 15 minutes, sera évaluée après chaque agent pendant une période de 2 et 4 heures. L'intervention sera limitée au premier agent hyperosmolaire reçu par chaque patient.

2.3 Les dispositions pratiques prévues pour la répartition des participants

Les participants seront randomisés dans chaque groupe, soit mannitol ou salin hypertonique avec une allocation 1 :1. Nous utiliserons une randomisation générée par ordinateur par notre statisticien, par blocs de 2 et de 4, stratifiée par centre. Le logiciel R sera utilisé pour la randomisation avec une semence (seed) spécifique pour assurer la reproductibilité de la liste de randomisation. Quatre centres sont prévus; deux centres auront un recrutement prévu de 4-5 patients par an et 2 centres de 7-8 patients par an. La randomisation sera gardée confidentielle par le statisticien du projet et des listes de chiffres pour randomisation seront envoyées aux pharmacies de chaque centre. L'éligibilité du patient et le consentement devront être effectués avant l'allocation du groupe assigné.

2.4 Les méthodes proposées pour éviter qu'il y ait des sources de biais
Les patients seront randomisés avec un système confidentiel tel que mentionné dans le paragraphe précédent. La pharmacie préparera pas la suite les solutions, à volume égaux dans des seringues opaques avec tubulures opaques. Malgré le fait que les deux solutions sont transparentes, le mannitol peut parfois avoir des micro-dépôts de sucre qui rendent la solution légèrement opaque. Il sera donc impossible d'identifier la solution au chevet du patient. L'infirmière au chevet, le médecin traitant, l'infirmière de recherche et la personne qui gère la base de données seront aveugles. De plus, l'issue primaire est une mesure objective et toutes co-interventions seront prises en compte.
Il se pourrait par contre que des patients soient randomisés mais ne reçoivent jamais l'intervention en question si leur PIC ne s'élève pas. Ceci engendrerait un biais non-différentiel puisque l'étude est randomisée et cet effet devrait se retrouver également dans chaque groupe, ce qui sera pris en compte dans notre calcul de taille d'échantillon. L'analyse se fera par Intention de traiter et par intention de traiter modifiée pour évaluer ces différences.

2.5 Les critères d'inclusion et d'exclusion prévus
Éligibilité : Le dépistage des patients se fera par l'équipe neurochirurgicale et/ou les soins intensifs, lors de l'évaluation du TCC sévère et de la mise en place d'un moniteur de PIC. L'infirmière de recherche sera ensuite contactée pour faire le consentement. Durant les heures non-ouvrables, un médecin de garde sera désigné au consentement du patient.
Inclusion : Tout patient de plus de 1 mois et moins de 18 ans, avec critères de TCC sévère (Glasgow < ou = 8), et mise en place de moniteur de PIC par la neurochirurgie, seront éligibles.
Exclusion : 1) tout patient avec mort cérébrale ou état moribond, 2) patients subissant une craniotomie décompressive 3) grossesse 4) hypernatrémie avec Na > 155 mosm/L (relative contre-indication salin 3%) 5) Osmolarité > 320mOsm/L (contre-indication mannitol) 6) Insuffisance rénale aigue sévère (contre-indication relative mannitol).

2.6 La durée prévue de la période de traitement
Les patients seront recrutés et randomisés dans les 48h suivant leur TCC. Une fois la décision d'administrer un agent hyperosmolaire après l'inclusion, le traitement sera donné en 20 minutes et le suivi de la pression intracrânienne se poursuivra pendant 4h post traitement.

2.7 La durée et la fréquence prévues du suivi
Les signes vitaux (FC, TA, diurèse) des patients seront recueillis aux 15 minutes pendant les deux heures après un agent hyperosmolaire, puis au 30 minutes jusqu'à quatre heures post agent hyperosmolaire. La PIC et la PPC seront récupérées directement du moniteur aux 5 secondes. Des bilans sanguins pour évaluer les électrolytes et la glycémie seront effectués à T240.

2.8 Les méthodes principales et secondaires proposées pour la mesure des résultats
Évènement principal étudié

L'évènement principal étudié sera la baisse de la pression intracrânienne entre les deux agents. Cette mesure se fait avec un moniteur de la pression intracrânienne en continu aux soins intensifs. Cette mesure étant continue et variable dans le temps, une moyenne des PIC notées aux 5 secondes sera calculée (T0 à T 120) et comparée à la PIC moyenne dans les 5 minutes avant d'initier le traitement hyperosmolaire (T-5 à T0)

Autres variable d'intérêt

Un calcul de la durée de la période où la PIC sera inférieure à 20 mmHg sera aussi effectuée afin d'évaluer de façon plus approfondie l'impact clinique futur de ces thérapies. Nous mesurerons aussi la pression de perfusion cérébrale (CPP), qui est la différence entre la tension artérielle moyenne (TA) et la PIC. Les complications des traitements : hypotension, hypovolémie et diurèse seront notées par l'infirmière dans le suivi pendant les 4h post traitement. L'hypernatrémie, la glycémie et l'acidose métabolique seront évaluées avec les prélèvements à T240.

2.9 De quelle façon la mesure des résultats se fera-t-elle lors du suivi ?

Dans les unités avec saisies de données électroniques, les valeurs de signes vitaux seront saisies automatiquement, puis rentrées dans une base de données par l'infirmière de recherche par la suite. Dans les centres où les données ne sont pas informatisées, l'infirmière de chevet sera chargée d'écrire les signes vitaux aux 15 minutes après l'intervention aux temps indiqués (tel que se fait de façon relativement standard aux heures dans les unités de soins intensifs). Une infirmière de recherche fera la saisie de données dans la base de données sur *Acces* par la suite.

2.10 L'essai englobera-t-il des sujets de recherche sur les services de santé ?

Ne s'applique pas

2.11 Taille proposée de l'échantillon

L'étude de Francony et al. démontre une baisse de la PIC de 45% +/- 19% pour le groupe mannitol et de 25% +/- 14% dans le groupe salin hypertonique[7]. Celle de Battison et al. rapporte une baisse de 59% avec le salin et de 31% avec le mannitol (12). Cliniquement, une baisse de la PIC de 5 mmHg est significative car il est bien reconnu que les dommages cérébraux sont significatifs lorsque la PIC reste de façon soutenue > 20 mmHg et sont plus importants > 25mmHg[15]. Selon cette littérature, il semble qu'une différence de 20% de la PIC soit cliniquement significative. Le calcul de la taille d'échantillon s'est fait en utilisant un *t-test* pour comparer 2 moyennes indépendantes. Les résultats de l'étude de Francony et al ont été utilisés comme moyenne pour chaque groupe ainsi que leur déviation standard afin de calculer un «effect size» de 1,198443. Un alpha à 0,05 et une puissance de 0,9 ont été utilisés. Il devra y avoir 13 patients par groupe, soit un total de 26 patients. Nous estimons, à la lumière d'une étude rétrospective dans notre centre que 20% des patients recrutés ne recevront pas d'agents hyperosmolaires et donc l'ajustement est fait pour 20% de plus, soit 26/0.8= 32,5 patients. Un nombre de 34 patients a été retenu pour être conservateur.

2.12 Quel est le taux de recrutement prévu ?

Nous savons qu'il y a actuellement 4-5 TCC pédiatriques sévères/année au CHU Sainte-Justine et au Montreal Children`s Hospital nécessitant une pose de PIC. À l'hopital

Sacré-Cœur et au Montreal General Hospital, deux centres adultes, ils comptent environ 7-8 TCC adolescents par années, pour un total des 4 centres d'environ 20 en étant conservateur. Compte tenu que nous voulons recruter 34 patients, nous devons prévoir une période de recrutement de 2 ans, en assumant qu'environ 85% des parents accepteront d'inclure leur enfant dans l'étude ((20 x 2) x0,85= 34).

2.13 Est-il probable qu'il y ait des problèmes d'inobservation ?
L'inobservance dans cet essai est peu probable puisque nous avons écourté la période d'observation à quatre heures seulement, dans le but de permettre aux cliniciens d'être à l'aise avec ce protocole. En effet, dans la réalité, les deux agents hyperosmolaires sont souvent administrés au même patient mais pas dans une courte période. De cette façon, les habitudes des cliniciens ne seront pas trop modifiées.

2.14 Quel est le taux probable de réduction de l'échantillon pendant le suivi ?
Comme il s'agit de patients aux soins intensifs et gravement malades observés sur une courte période de temps, il y a peu de chances de perdus de vue. En effet, il pourrait y avoir un certain nombre de décès, mais ceux-ci surviennent généralement plus tard que dans la courte fenêtre utilisée.

2.15 Le nombre de centres participant à l'essai
Les quatre centres inclus sont les centres principaux pour la prise en charge neurochirugicale du trauma crânien de l'enfant au Québec. Tous se situent dans la ville de Montréal. Deux centres sont désignés pédiatriques et les deux autres sont des centres adultes de traumatologie qui incluent des adolescents < 18 ans dans leur clientèle.

2.16 Quel est le type d'analyse proposé ?
Les données seront entrées dans la base de données par les infirmières de recherche et validées par les chercheurs principaux. Par la suite, un statisticien indépendant fera les analyses à l'aide du logiciel SPSS version 21.
Les analyses concernant l'issue primaire et les issues secondaires seront d'abord effectuées selon l'intention de traiter (ITT). Cependant, si le nombre de patients inclus qui n'ont pas reçu de traitement est plus important que celui prédit (20%), nous devrons faire des analyses en intention de traiter modifiée. Un niveau alpha de 5% sera utilisé comme seuil de significativité pour toutes les analyses. D'abord, les caractéristiques de base (âge, genre, poids, osmolarité sanguine et natrémie avant et après traitement, PIC à l'installation du moniteur, PIC avant le traitement hyperosmolaire, durée séjour hospitalier, durée séjour aux soins intensifs, mortalité) dans les 2 groupes seront comparées à l'aide du *test t* pour échantillon indépendants, ou du Mann Whitney pour les variables continues, et du Khi-2 de Pearson pour les variables catégorielles. Par la suite, l'issu primaire sera mesurée par la différence entre la PIC avant le traitement et la moyenne de PIC dans les deux heures suivant le traitement (Δ PIC) en pourcentage (Δ PIC/Pic initiale). Il sera calculé pour chaque patient et les résultats seront comparés à l'aide du *test t* pour échantillons indépendants si la distribution est normale ou Mann Whitney si elle ne l'est pas. Pour les issus secondaires, le même calcul sera fait avec les données dans les 4 heures suivant le traitement. Ce même calcul sera aussi fait pour la pression de perfusion cérébrale. Finalement, il y a aura une comparaison entre les effets

secondaires mais le nombre de patients étant limitées, ces analyses n'auront pas beaucoup de valeur autre que de faire ressortir un effet secondaire très fréquent.

2.17 Quelle fréquence est proposée pour les analyses ?
Comme il s'agit d'une étude pilote avec un petit nombre de patients, nous ne ferons pas d'analyse intérimaire. Toutes les analyses seront faites à la fin de l'étude.

2.18 Est-il prévu de faire des analyses de sous-groupes ?
Chaque analyse sera stratifiée par centre. Cependant, il n'y aura pas d'analyse de sous-groupe car le nombre de participants est assez petit ce qui ne nous permettrait pas d'avoir une bonne puissance statistique.

2.19 Des études pilotes recourant à la même méthodologie ont-elles été menées ?
Pour le moment il n'y a aucune étude pédiatrique qui a utilisé la même méthodologie. Cette étude sera en quelque sorte l'étude pilote qui nous permettra, selon les résultats, de monter un devis différent afin d'évaluer l'efficacité clinique au long cours de l'un ou l'autre des ces agents hyperosmolaires.

3. GESTION DE L'ESSAI

3.1 Quelles dispositions sont prévues pour la gestion quotidienne de l'essai ?
L'investigateur principal et le co-investiguateur, ainsi que le centre coordinateur le CHU Sainte-Justine, seront responsables de la gestion de l'étude. La gestion de la base de données sera effectuée par le CHU-Sainte Justine.
Une infirmière de recherche dans chaque site sera disponible sur appel pour discuter avec les parents et faire signer le consentement pendant la journée. Comme il y a peu de cas de traumatisme crânien sévère dans chaque centre, nous ne pouvons pas nous permettre de recruter seulement les jours de semaine. Chaque infirmière aura donc une semaine de garde/mois où elle devra être disponible pour venir faire le consentement la nuit ou la fin de semaine au besoin si le médecin de service est trop occupé pour le faire. Elle sera de garde pour les quatre centres et recevra une rémunération pour être de garde et un bonus pour chaque déplacement effectué. Elles seront aussi responsables de recueillir toutes les données pendant les 4 heures après le bolus et de les mettre dans la base de données *Acces* qui sera conservée sur un serveur sécurisé.
Le pharmacien de chaque site s'occupera de la préparation de la médication. Pendant la nuit, les pharmaciens de garde recevront un forfait spécial s'ils doivent se déplacer pour l'étude seulement.

3.2 Le rôle de chacun des candidats et co-candidats proposés
Dre Roumeliotis et Dre Morissette seront responsables de la gestion de la recherche au jour le jour. Elles seront aussi en charge de l'interprétation des résultats de l'étude et de la rédaction du/des articles. Il y aura un responsable de la coordination dans chaque site qui sera choisi parmi les médecins ayant un intérêt spécifique pour le TCC et la recherche aux soins intensifs. Le statisticien sera responsable de l'analyse statistique des données intérimaires et finales de l'étude

3.3 Description du comité de direction et du comité de surveillance et de protection des données

Le comité de direction sera constitué de 4 experts en soins intensifs, soit 2 en médecine adulte et 2 en pédiatrie. Il y aura un neurochirurgien, un pharmacien et un expert en analyse statistique et méthodologie.

Le comité de surveillance sera constitué de 4 experts en soins intensifs, soit 2 en médecine adulte et 2 en pédiatrie. Il y aura un neurochirurgien, un pharmacien et un expert en analyse statistique et méthodologie.

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